PHARMACOTHERAPY REVIEW
NARCOTIC ANALGESICS

I. INTRODUCTION

Successful pain management is an **attainable goal** for the **majority** of patients with **acute** or **chronic pain**. However, **achievement** of that goal may be **difficult**, particularly when the pain is **severe** and **chronic** in nature. It is well recognized that **patient response** to different analgesics can be **highly variable**. A particular analgesic dose that produces successful pain relief in one patient may produce intolerable adverse effects and inadequate pain control in another individual.

Successful pain management requires knowledge of a variety of analgesic agents, whom to treat with what, when to treat, how to match analgesic therapy to pain severity, available analgesic delivery systems, appropriate dosage levels for initiation of therapy and titration, appropriate indications, contraindications and "black box" warnings, precautions to observe relative to risk factors, the adverse drug reaction and drug interaction potential of various agents, the potential of analgesic agents to produce tolerance to their analgesic effectiveness, the potential of narcotic analgesics to produce physical dependency and addiction and the overuse, misuse and/or abuse potential of various agents.

This review addresses the **narcotic analgesics** in the management of **moderate** to **severe acute** and **chronic pain**, taking into account the above mentioned factors.

Selected pharmacological properties of the narcotic analgesics are presented below.

SELECTED PHARMACOLOGICAL PROPERTIES OF NARCOTIC AGONISTS

Drug	Analgesic	Antitussive	Constipation	Respiratory Depression	Sedation	Emesis	Physical Dependence
Phenanthrenes							
Codeine	+	+++	+	+	+	+	+
Hydrocodone	+	+++	nd[1]	+	nd[1]	nd[1]	+
Hydromorphone	++	+++	+	++	+	+	++
Levorphanol	++	++	++	++	++	+	++
Morphine	++	+++	++	++	++	++	++
Oxycodone	++	+++	++	++	++	++	++
Oxymorphone	++	+	++	+++	nd[1]	+++	+++
Phenylpiperidines							
Fentanyl	++	nd[1]	nd[1]	+	nd[1]	+	nd[1]
Meperidine	++	+	+	++	+	nd[1]	++
Diphenylheptanes							
Levomethadyl	++	nd[1]	++	nd[1]	nd[1]	+	+
Methadone	++	++	++	++	+	+	+
Propoxyphene	+	nd[1]	nd[1]	+	+	+	+

[1] nd = no data available
Adapted with permission from Drug Facts and Comparisons, June, 2003

Selected pharmacokinetic properties of the narcotic analgesics are presented below.

PHARMACOKINETICS OF NARCOTIC AGONISTS				
Drug	**Onset (minutes)**	**Peak (hours)**	**Duration[2] (hours)**	**T½ (hours)**
Codeine	10 to 30	0.5 to 1	4 to 6	3
Fentanyl (inj.)	7 to 8	nd	1 to 2	1.5 to 6
Hydrocodone	nd	nd	4 to 6	3.3 to 4.5
Hydromorphone	15 to 30	0.5 to 1	3 to 5	2 to 3
Levomethadyl	2 to 4 hrs	1.5 to 2	48 to 72	2 to 6 days
Levorphanol	30 to 90	0.5 to 1	6 to 8	11 to 16
Meperidine	10 to 45	0.5 to 1	2 to 4	3 to 4
Methadone	30 to 60	0.5 to 1	4 to 8	15 to 30
Morphine	15 to 60	0.5 to 1	3 to 7	1.5 to 2
Oxycodone	15 to 30	1	4 to 6	3.5 to 5
Oxymorphone	5 to 10	0.5 to 1	3 to 6	nd
Propoxyphene (PO)	30 to 60	2 to 2.5	4 to 6	6 to 12

nd = no data available
Adapted with permission from Drug Facts and Comparisons, June, 2003.

The **non-injectable narcotic analgesics evaluated** are included in the table below.

NON-INJECTABLE NARCOTIC ANALGESICS EVALUATED			
DEA Schedule	**DRUG**	**STRENGTH (mg)**	**DOSAGE FORM**
IV	Butorphanol (Stadol NS)	10/ml	nasal spay
		1 mg/spray	
III	Buprenorphine (Subutex)	2	Tab (SL)
		8	Tab (SL)
II	Codeine (Multisource)	15	Tab
		30	Tab
		60	Tab
		15/5ml	Soln
II	Hydromorphone (Multisource; Dilaudid)	1	Tab
		2	Tab
		3	Tab
		4	Tab
		8	Tab
		5/5ml	Liq
II (as single entity) III (as combination)	Hydrocodone (Available only in oral combination with other drugs in U.S.)		

DEA Schedule	DRUG	STRENGTH (mg)	DOSAGE FORM
II	Levomethadyl (ORLAAM)	10/ml	Soln
II	Levorphanol (Levo-Dromoran)	2	Tab
II	Fentanyl Transdermal System (Duragesic)	2.5	Patch
		5	Patch
		7.5	Patch
		10	Patch
II	Fentanyl Transmucosal (Fentanyl Oralet)	100 mcg	Loz
		200 mcg	Loz
		300 mcg	Loz
		400 mcg	Loz
II	Fentanyl Transmucosal (Actiq)	200	Loz
		600	Loz
		800	Loz
		1200	Loz
		1600	Loz
II	Meperidine (Multisource; Demerol)	50	Tab
		100	Tab
		50/5 ml	Syrup
II	Methadone	5	Tab
		10	Tab
		40	Tab
		5/5 ml	Soln
		10/5 ml	Soln
		10/ml	Liq.Conc.
II	Morphine SO_4 (MS Contin; Oramorph SR) ▪ Currently requires Prior Authorization	15	Tab (CR)
		30	Tab (CR)
		60	Tab (CR)
		100	Tab (CR)
II	Morphine SO_4 (MS Contin) ▪ Currently requires Prior Authorization	200	Tab (CR)
II	Morphine SO_4 (Kadian) ▪ Currently requires Prior Authorization	20	Cap (SR)
		30	Cap (SR)
		50	Cap (SR)
		60	Cap (SR)
		100	Cap (SR)
II	Morphine SO_4 (Multisource) ▪ Currently requires Prior Authorization	15	Tab (ER)
		30	Tab (ER)
		60	Tab (ER)
		100	Tab (ER)
II	Morphine SO_4 (MSIR; Multisource)	15	Tab
		30	Tab
II	Morphine SO_4 (MSIR)	15	Cap
		30	Cap
II	Morphine SO_4 (MSIR; Multisource)	10/5 ml	Soln
		20/5 ml	Soln
		20/ml	Soln

DEA Schedule	DRUG	STRENGTH (mg)	DOSAGE FORM
II	Morphine SO_4	100/5 ml	Soln
II	Morphine SO_4 (RMS; Multisource)	5	Supp
		10	Supp
		20	Supp
		30	Supp
II	Oxycodone (Roxicodone; Multisource)	5	Tab
II	Oxycodone (Roxicodone)	15	Tab
		30	Tab
II	Oxycodone (OxyIR; Multisource)	5	Cap
II	Oxycodone (Roxicodone)	5/5 ml	Soln
II	Oxycodone (Roxicodone Intensol; Oxycodone; OxyFast)	20/ml	Soln (Conc.)
II	Oxycodone SR (OxyContin) ▪ Currently Requires Prior Authorization	10	Tab (CR)
		20	Tab (CR)
		40	Tab (CR)
		80	Tab (CR)
		160	Tab (CR)
II	Oxymorphone (Numorphan)	5	Supp
IV	Propoxyphene (Darvon-N)	100	Tab
IV	Propoxyphene (Darvon; Multisource)	65	Cap
IV	Pentazocine (available only in oral combinations with other drugs in the U.S.)	---	---
---	Tramadol (Ultram; multisource)	50	Tab

II. PAIN DEFINITION

The International Association for the Study of Pain (IASP) defines pain as… An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of damage.[1]

Pain is generally **categorized** as **acute** or **chronic**. **Acute pain** is typically of short duration, and immediate-release analgesic agents typically manage acute pain quite well. **Chronic pain** is complex, often difficult to treat, and may require high doses of narcotic analgesics over prolonged periods of time.

Most often **acute pain** is **nociceptive** (i.e. caused by a response to a noxious stimulus such as trauma, heat, extreme cold, chemical, pressure, etc.). **Chronic pain** can also be **nociceptive**, but may also be **neuropathic** (i.e. initiated by a primary lesion or dysfunction in the nervous system) or **mixed** in origin.

III. OPIOID ACTION

Opioid agonists are the **current standard** therapies for managing **moderate to severe pain of an acute or chronic nature**. Opioids bind and activate receptors that operate to modulate pain. Opioid receptors are found in inhibitory pain circuits that descend from the midbrain to the spinal cord dorsal horn.[2] Opioid receptors also exist in the peripheral nervous system.

Opioid receptors consist of three subtypes: mu, delta, and kappa. Most of the effective opioid agonists (prototype is morphine) are relatively selective for mu receptors. These analgesic drugs also affect mood, behavior, and can alter respiratory cardiovascular, gastrointestinal and neuroendocrine functions. **Full agonists** have **no ceiling** to their **analgesic effects**, but **dosing is limited** by **drug-induced adverse effects**.

Patient **analgesic response** to opioids is **highly variable**. The World Health Organization (WHO) has established a three step **pain management algorithm** (the WHO Analgesic Ladder) for cancer pain based on severity of pain: **Step I** addresses **mild to moderate pain** manageable with **aspirin, APAP or NSAIDs**. **Step II** addresses **moderate to moderately severe pain** with use of **opioid agonists** such as **codeine, hydrocodone and oxycodone**. **Step III** addresses **severe pain** utilizing **morphine, oxycodone, hydromorphone, methadone**, or **fentanyl**.[3] **Adjuvant analgesics** may be added to **enhance analgesic effectiveness**.

IV. ROUTE OF ADMINISTRATION

The **route of analgesic administration** selected should be the **safest** and **least invasive** method that will produce **effective analgesia**. The **oral route is preferred** because it is the most **convenient, inexpensive** and **easiest to titrate**.[4] For patients who cannot swallow or have other complicating pathology (i.e., g.i. obstruction) other routes may be employed (e.g., transdermal, rectal).

V. INDICATIONS

Not all non-injectable narcotic analgesics have the same indication. The **indications** for the **products evaluated** are **included below**.

DRUG	INDICATION(s)
Butorphanol (NS)	moderate to severe pain; post operative analgesia
Buprenorphine (SL TAB)	opioid dependence only (injectable used for moderate to severe pain)
Codeine (TAB; SOLN)	mild to moderate pain; cough suppression
Hydromorphone (TAB; SOLN)	moderate to severe pain
Hydrocodone (in combination with other analgesics (TAB; CAP; ELIXIR)	moderate to severe pain
Levomethadyl (SOLN)	opioid dependence only
Levorphanol (TAB)	moderate to severe pain; preoperative analgesia
Fentanyl (TRANSDERMAL)	Chronic pain management in patients requiring continuous opioid analgesia to manage moderate to severe pain that cannot be managed by lesser means (i.e., short acting oral opioids, NSAIDs or opioid-APAP combinations).

DRUG	INDICATION(s)
Fentanyl (TRANSMUCOSAL)	breakthrough cancer pain (Actiq only) in patients who are already receiving and tolerant to opioid therapy (i.e., ≥ 60 mg morphine per day, 50 mcg transdermal Fentanyl per hour or an equianalgesic dose of another opioid for ≥ 1 week.
Fentanyl (TRANSMUCOSAL)	anesthetic premedication in a hospital setting (Fentanyl Oralet)
Meperidine (TAB; SYRUP)	moderate to severe pain
Methadone	severe pain; detoxification treatment of narcotic addiction; temporary maintenance treatment of narcotic addiction.
Morphine sulfate immediate-release (TAB;CAP; SOLN)	moderate to severe pain
Morphine sulfate (SUPP)	severe pain
Oxycodone: immediate-release (TAB;CAP; SOLN)	moderate to severe pain where use of an opioid analgesic is appropriate
Oxymorphone (SUPP)	moderate to severe pain; preoperative medication support of anesthesia; obstetrical analgesia
Propoxyphene (TAB; CAP)	mild to moderate pain
Pentazocine (in combination with other analgesics) [TAB]	moderate to severe pain
Tramadol (TAB)	moderate to moderately severe pain

NOTE:

Opioid agonists are classified as (1) full agonist, (2) partial agonists and (3) mixed agonists/antagonists.

Full agonists have **no ceiling** to their **analgesia**, thus doses are determined by an adequate pain response or dose-limiting adverse effects occur.[5] Narcotic analgesics in this report that are **full agonists** are listed below.

codeine
hydromorphone
hydrocodone
levomethadyl
levorphanol
fentanyl
meperidine
methadone
morphine
oxycodone
oxymorphone
propoxyphene
tramadol

Partial agonists (i.e. buprenorphine) and **mixed agonist/antagonists** (i.e., butorphanol, pentazocine) have a **ceiling** on their **analgesic** effect that is **roughly equivalent** to **moderate doses** of **full agonists (above)**. For **moderately severe to severe chronic pain**, the **full agonists are preferred** over the **partial agonists** and **mixed agonists/antagonists** narcotics.

Tramadol is classified as a **centrally acting opioid**. Its **effectiveness** is **comparable** to that of **combinations** of **aspirin or acetaminophen with propoxyphene or codeine**. [6]

Levomethadyl must be dispensed only by an Opioid Treatment Program certified by SAMHSA under 42 CFR, Part 8 and registered by the DEA under 21.USC 823(g) (1).

VI. CONTRAINDICATIONS

Few **absolute contraindications** to narcotic analgesics exist. The contraindications common to the class include the following:

a. Hypersensitivity to the narcotic analgesic or adhesives of transdermal formulations.
b. Acute or severe asthma
c. Upper airway obstruction
d. Significant respiratory depression
e. Use in premature infants
f. Labor and delivery of a premature infant

VII. "BLACK BOX" WARNING, PRECAUTIONS AND INDIVIDUAL PATIENT RISK FACTORS [6, 7]

"Black Box" warnings on the full agonist, **transmucosal fentanyl**, and **methadone** are particularly noteworthy. **Transmucosal fentanyl (Actiq)** is indicated for **breakthrough cancer pain only** in **patients already receiving** and **tolerant to opioids**. This drug may induce **life-threatening hypoventilation (respiratory depression)** in **patients not taking opioid analgesics**. Transmucosal fentanyl is **NOT** to be used in **opioid non-tolerant patients.** This drug is **NOT** to be used to treat **acute** or **post-operative pain**. **Use** should be **restricted** to **oncologists** and **pain management specialists** skilled in the use of Schedule II opioids to treat cancer pain. **Lozenges resemble suckers** that could be **fatal to a child**.

Methadone used as an **analgesic** may be **dispensed** in **any licensed pharmacy**, but can only be dispensed by **pharmacies designated/approved** by the **FDA** and **state authorities if used** to **manage narcotic addiction** and **detoxification** or **maintenance therapy** (Federal Methadone Regulations 21 CFR 291.505).

Black box warnings on **oxycodone only apply** to the **controlled-release dosage forms** (currently under an Alabama Medicaid prior authorization [PA] requirement).

Beyond "black box" warnings, the following facts deserve specific consideration.[5, 6, 7]

- All narcotic analgesics may induce **cognitive impairment** and **impair motor skills,** especially when therapy is initiated or during dosage escalation.
- **Hydromorphone** may **increase CSF pressure.**
- **Hydromorphone** may cause **transient hyperglycemia**
- **Methadone** and **meperidine** enter **breast milk** in **concentrations** approaching **plasma levels**
- The **placental transfer** of **narcotics** is **rapid**. Neonatal withdrawal from maternal addiction usually develops in the first day of life.
- **Fentanyl Transdermal** is **not indicated** in **children <12 years of age or patients <18 years of age who weigh <50 kg** except in authorized research.
- **Most opiate narcotics** are **not indicated** in **children**
- **Narcotics** may **obscure** the **diagnosis** of **acute abdominal conditions.**
- **Therapeutic doses** of narcotics may **decrease pulmonary ventilation**, thus debilitated patients, elderly patients and patients with cardiopulmonary conditions require **special considerations** relative to **dose** and **monitoring.**

- **Additional special risk patients** who should be medicated very carefully with opioid narcotics are those who suffer from conditions accompanied by **hypoxia** and **hypercapnia, sensitivity to CNS depressants, cardiovascular disease, renal and/or hepatic disease, seizure disorders, increased intracranial or ocular pressure, acute alcoholism, delirium tremens, cerebral arteriosclerosis, fever, decreased respiratory reserve, sleep apnea, inflammatory bowel disease, pseudomembranous colitis, g.i. hemorrhage, hypothyroidism, Addison's disease, prostatic hypertrophy, uretheral stricture, gall bladder disease or recent g.i. or g.u. surgery.**
- The **conversion protocol** included in package labeling should be used when converting a patient from **morphine** to **transdermal fentanyl**.
- **Morphine** has **no greater dependence liability** that **equally effective doses** of any **other full agonists**.
- **Repeated doses of meperidine** can lead to **accumulation** of **normeperidine,** a **toxic metabolite** with a **15 to 20 hour half-life**. This metabolite can produce dysphoria, irritability, tremors and occasionally seizures. Risk is increased with decreased renal function. The **American Pain Society** recommends that **meperidine** be used only for **short-term** treatment of **acute pain.**[8]
- **Seizures** have been reported in patients taking **tramadol**. Patients with a history of seizures and those taking an antidepressant, an MAO inhibitor or an antipsychotic drug appear to be at increased risk.
- **Tramadol** is **not scheduled** as a controlled substance, but **opioid-type dependence has occurred**.
- **Drug addiction** and **abuse** are a documented **problem** with the use of **butorphanol nasal spray off label** for treatment of **migraine**.[6]
- **Codeine** alone at an oral dosage of **60 mg** is **equivalent** in **analgesic** effect to **650 mg of aspirin or acetaminophen**.
- **Fentanyl transdermal** system appears to produce **less constipation** than **morphine**.
- The **long half-life** of **methadone increases risk** of **CNS depression** when **dosed repeatedly for pain.**
- **Propoxyphene, 65 mg** as HCl and **100 mg** as napsylate are **equivalent** to **32 mg** of **codeine** when used **orally** as an **analgesic.**
- **Levorphanol** has a **long half-life** and **risk** of significant **CNS depression** with **repeated use**.

VIII. ADVERSE EFFECTS [4-7, 10-12]

Secondary pharmacological effects (non-analgesic pharmacological effects) from the narcotic analgesics are considered undesirable adverse effects. These can involve the following body systems:

Cardiovascular System
Central Nervous System
Gastrointestinal System
Genitourinary System
Respiratory System
Skin
Endocrine System

The **most serious adverse effects** are associated with respiratory depression and circulatory depression. Worst case manifestations would be apnea, respiratory arrest, shock, coma, hypoventilation and cardiac arrest.

The **most frequently occurring adverse effects** associated with the narcotic analgesics are sedation, cognitive impairment, dizziness, nausea, vomiting, itching and constipation. Tolerance usually develops to the sedative and emetic effects of the narcotic analgesics, but not to the constipation. A stool softener administered daily is recommended if therapy with the narcotic is expected to be chronic. One study has shown that transdermal fentanyl caused less sedation and constipation than sustained-release oral morphine.[9]

Selected other adverse effects by system to the narcotic analgesic **class as a whole** are included below:

Cardiovascular: flushing, tachycardia, bradycardia, arrhythmia, palpitations, changes in blood pressure (both increased and decreased), orthostatic hypotension and syncope.

CNS: euphoria, dysphoria, delirium, insomnia, agitation, anxiety, disorientation, drowsiness, sedation, lethargy, decreased cognition, uncoordinated movements, weakness, mental clouding, hallucinations, blurred vision, miosis, depression, nightmares and apathy.

Gastrointestinal: nausea, vomiting, diarrhea, cramps, abdominal pain, dry mouth, anorexia, constipation, biliary tract spasm, dysphagia, and gastroesophageal reflux.

Genitourinary: ureteral spasm, spasms of vesicle sphincters, urinary retention or hesitancy, oliguria, antidiuretic effect, reduced libido or potency, impotence, difficulty urinating, dysuria and urinary incontinence.

Dermatologic: pruritus, urticaria, hives, facial swelling, itching and edema.

Miscellaneous: depression of cough reflex, difficulty with thermal regulation, chills, skeletal muscle rigidity (neck and extremities), exacerbation of asthma, bronchospasm, laryngospasm, rhinitis, arthralgia, hot flashes, hiccups, nasal congestion, rhinorrhea, hyperglycemia, elevated CPK level.

Other adverse effects and more severe adverse effects may occur and are more likely at high doses. Patients on narcotic analgesics must be carefully monitored for drug-induced adverse events.

IX. DRUG INTERACTIONS

A variety of **drug interactions** may occur between narcotic analgesics and other drugs. Awareness of these drug interactions is the key. Interacting drug may be co-administered in some cases if proper dosing adjustments are made. In other cases, the non-narcotic drug may be discontinued or replaced by a therapeutically similar agent without interaction potential. The more relevant interactions between narcotic analgesics and other drugs are included below.

Drug Interactions		
Precipitant Drug	**Object Drug***	
Agonist/Antagonist analgesics	Narcotic agonist analgesics	↓
Chlorpromazine Thioridazine	Narcotic agonist analgesics	↑
MAOIs	Narcotic agonist analgesics	↑
Antihistamines Methocarbamol	Morphine	↑
Amitriptyline	Morphine	↑
Cimetidine	Meperidine Methadone Morphine	↑
Clomipramine	Morphine	↑
Diazepam	Fentanyl	↑
Fluvoxamine	Methadone	↑
Hydantoins	Meperidine Methadone	↓
Nortriptyline	Morphine	↑
Protease inhibitors	Fentanyl Hydrocodone Meperidine Methadone Ocycodone Propoxyphene	↑
Rifampin	Methadone	↓
Methadone	Desipramine	↑
Morphine Propoxyphene	Anticoagulants	↑
Propoxyphene	Carbamazepine	↑

* ↑ = Object drug increased ↓ = Object drug decreased

Adapted with permission from Drug Facts and Comparisons, June, 2003.

X. TOLERANCE

Tolerance to analgesic effect of chronic opioid use necessitates increasing the dose over extended periods to maintain pain management. Tolerance to many of the opioid-induced adverse effects also occurs (with the exception of constipation).

XI. PHYSICAL DEPENDENCE V. ADDICTION

Physical dependence and addiction are terms that should not be used interchangeably. There are distinct differences.

Addiction is psychological dependence on the use of chemical substances for their psychic effect (e.g., euphoria, grandiosity, detachment from reality). Addiction is associated with a loss of control over drug use and compulsive drug use despite the risk and harm. Clear indicators of addiction and substance abuse include prescription forgeries, theft of prescription pads, theft/burglary of drugs, seeing multiple physicians, requests for early refills and compulsive drug use. Rates of drug abuse and addiction among chronic, non-cancer pain sufferers has been estimated to be between 3.2% and 18.9%.[13]

Physical dependency is a normal and expected response to appropriate medical use of narcotic analgesics over a prolonged period of time. Physical dependency is NOT a manifestation or component of addiction. Physical dependency does not pose a clinical problem unless the dose of a narcotic analgesic taken chronically is tapered too quickly or abruptly discontinued. Patients do need to be warned of this risk. Excessively rapid tapering of doses or withdrawal of chronically administered narcotics will lead to a withdrawal/abstinence syndrome characterized by symptoms such as anxiety, irritability, chills, hot flashes, arthralgia, rhinorrhea, lacrimation, sweating, nausea, vomiting, diarrhea, abdominal cramps and sleep disturbances.

XII. RECOMMENDATIONS

Introduction [15]

The American Pain Society estimates that each year 50 million people suffer from severe chronic pain and another 25 million experience self-limited acute pain from injuries or surgery.[15] It has been stated that **acute, self-limited mild to moderate pain** is **overtreated** with **narcotic analgesics** while **NSAIDs, acetaminophen and aspirin** are **underutilized** by prescribers, **but moderate to severe acute self-limited pain** and **chronic nonmalignant and malignant pain** is frequently **undertreated**.

A **robust therapeutic armamentarium** of appropriate narcotic analgesics, as **multisource single entities** and **combination therapies** is **available** to **manage** the **full spectrum of pain**.

Single Entity Narcotic Analgesics

The following **single entity narcotic analgesics** are **multisource** and are automatically **exempted** from any **prior authorization requirement**.

Single Entity Narcotic Analgesics			
DEA Schedule	**Drug**	**Strength (mg)**	**Dosage Form**
II	Codeine	15	Tab
		30	Tab
		60	Tab
		15/5 ml	Soln
II	Hydromorphone	1	Tab
		2	Tab
		3	Tab
		4	Tab
		8	Tab
		5/5 ml	Liq
II	Meperidine	50	Tab
		100	Tab
		50/5 ml	Syrup
II	Morphine SO4	15	Tab
		30	Tab

Single Entity Narcotic Analgesics (cont'd)			
DEA Schedule	**Drug**	**Strength (mg)**	**Dosage Form**
II	Morphine SO4	10/ 5 ml	Soln
		20/ 5 ml	Soln
		20/ml	Soln
II	Morphine SO4	5	Supp
		10	Supp
		20	Supp
		30	Supp

No additional brand name **single entity narcotic analgesics offer** any **significant clinical advantages** over the drugs, strengths and dosage forms listed above for **general use** in managing **moderate to severe acute and chronic pain.** Narcotic analgesics that offer **special characteristics** in **dosage forms/delivery system** (e.g. transmucosal, transdermal, intranasal, sublingual, oral solid sustained-release) should be considered products available for **special needs/circumstances** that require **medical justification** through the **prior authorization** process. After **clinical circumstances** are **explored, proper medical justification** will **provide patient access** to **narcotic analgesics** with **special dosage form/delivery system characteristics.**

Brand name single entity narcotic analgesics can be considered for preferred status if the price of the brand name agent is competitive to a pharmaceutically and therapeutically equivalent multisource (generic) formulation. The price competitive point will be determined by Alabama Medicaid.

Thus, no brand name, single entity narcotic analgesics are recommended for preferred drug status.

COMBINATION NARCOTIC ANALGESICS

Combination narcotic agents are typically assigned **schedule III** or **schedule IV** status. They should be **held in reserve** for the treatment of **mild to moderate, acute, self-limited pain unless** therapy with **NSAIDs** and/or **APAP** or **ASA fail**. **A therapeutic pain management failure** with **NSAIDs, APAP or ASA** or pain in the **moderate to moderately severe range warrants** schedule III and schedule IV **combination narcotic analgesic therapy** in **most instances**. **Moderate to severe, chronic, non-cancer, cancer or neuropathic pain** may require a **schedule II full opioid agonist.**

In **combination narcotic analgesics** the narcotic is **combined** with **adjuvant analgesics** (e.g., acetaminophen, aspirin) in order to **achieve an additive** or enhanced **analgesic effect.**

Most combination narcotic analgesics are available in **generic versions**. Clinicians are encouraged to be ever mindful of the **overuse, misuse, abuse, addiction-potential and diversion** associated with **all narcotic analgesics**, but **particularly** the **combination narcotic analgesics** in their generic or brand (e.g., Lortab, Vicodin, Percocet, Tylox, Perdocan) form.

The following **combination narcotic analgesics** are **standard therapies** for **general use**, **multisource,** and automatically **exempted** from any **prior authorization requirement.**

Combination Narcotic Analgesics			
DEA Schedule	**Drug**	**Strength (mg)**	**Dosage Form**
V	Codeine/APAP (**multisource**)	12/120	Soln
III	Codeine/APAP (**multisource**)	15/300	Tab
III	Codeine/APAP (**multisource**)	30/300	Tab
III	Codeine/APAP (**multisource**)	60/300	Tab
III	Codeine/ASA (**multisource**)	30/325	Tab
III	Codeine/ASA (**multisource**)	60/325	Tab
III	Hydrocodone/APAP (**multisource**)	5/500	Cap
III	Hydrocodone/APAP (**multisource**)	5/500	Tab
III	Hydrocodone/APAP (**multisource**)	7.5/500	Tab
III	Hydrocodone/APAP (**multisource**)	10/650	Tab
III	Oxycodone/APAP (**multisource**)	5/325	Tab
III	Oxycodone/APAP (**multisource**)	5/500	Cap
III	Oxycodone/APAP (**multisource**)	4.5/.38/325	Tab
IV	Propoxyphene Nap/APAP (**multisource**)	100/650	Tab
IV	Propoxyphene HCl/APAP (**multisource**)	65/650	Tab

No additional brand name, **combination narcotic analgesics offer** any **significant clinical advantages** over the drug, strengths and dosage forms listed above for **general use** in managing **mild to moderate, acute, self-limited pain when therapy with NSAIDs, APAP or ASA fail.** The **prior authorization** process does, however, **provide access** to brand name drugs if **proper medical justification** is **provided**.

Brand name combination narcotic analgesics can be considered for preferred status if the price of the brand name agent is competitive to a pharmaceutically and therapeutically equivalent multisource (generic) formulation. The price competitive point will be determined by Alabama Medicaid.

Thus, no brand name, combination narcotic analgesics are recommended for preferred drug status.

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1. Antiplatelet Agents

A. Overview: The following table displays the various characteristics of the five antiplatelet agents primarily discussed in this report.

Characteristic	ASA[1]	Clopidogrel[2]	Ticlopidine[3]	ASA/DP-ER*[4]	Dipyridamole[5]
Brand Name	Aspirin	Plavix	Ticlid	Aggrenox	Persantine
Brand Manufacture	Bayer	Sanofi, BMS	Syntex/Roche	Boehringer Ingelheim	Boehringer Ingelheim
Generic available	Yes	No	Yes	No	Yes
Pharmacology	Irreversibly inhibits platelet cyclo-oxygenase; inhibits thromboxane A2 production (inducer of platelet aggregation and vasoconstriction)	Irreversibly inhibits binding of adenosine diphosphate (ADP) to its platelet receptor and subsequent activation of the glycoprotein IIb/IIIa complex	Interferes with platelet membrane function by inhibiting ADP-induced platelet fibrinogen binding and subsequent platelet-platelet interactions	See ASA and dipyridamole	Inhibits adenosine influx into platelets, endothelial cells and erythrocytes; results in stimulation of platelet adenylate cyclase and increases platelet cyclic-3',5'-AMP
FDA-Approved Indications	Prophylaxis of: TIA; cerebral thromboembolism; MI; reinfarction in patients with unstable angina	Reduction of atherothrombotic events: 1) recent MI, recent stroke or established peripheral artery disease (PAD) and 2) acute coronary syndrome (unstable angina/non–Q-wave	Reduce risk of thrombotic stroke in patients with precursors, and in patients with completed thrombotic stroke. Also as adjunctive therapy with ASA to reduce incidence	Reduce stroke in patients with TIA of the brain or completed ischemic stroke due to thrombosis	Adjunct to warfarin to prevent postoperative thromboembolic complications associated with the placement of mechanical heart valves

		MI) including patients who are to be managed medically and those who are to be managed with PCI, with or without stent, or CABG	of subacute stent thrombosis in patients undergoing successful coronary stent implantation		
Unlabeled Drug Uses	Cerebral recurrent thromboembolism; TIA; cerebrovascular embolism, stroke[1]		Alternative to ASA for various disease states (e.g., unstable angina, angioplasty); combined with ASA for various selected patients[6]		Multiple unlabeled uses in combination with ASA[6,7]

Characteristic	ASA	Clopidogrel	Ticlopidine	ASA/DP-ER*	Dipyridamole
Dose	80-325 mg once daily (specific dose depends upon disease state)	75 mg once daily in patients with recent MI, recent stroke or established PAD 300 mg LD followed by 75 mg once daily to treat acute coronary syndrome. LD should be administered ≥ 6 hours prior to PCI.[36,37]	250 mg BID to reduce the risk of thrombotic stroke 250 mg BID in conjunction with ASA (75-325 mg daily) to prevent coronary artery stent thrombosis	One capsule BID	75-100 mg QID (thromboembolism after cardiac valve replacement) 75 mg TID-QID (thromboembolism in patients with prosthetic heart valve and contraindication to anticoagulants) 225-400 mg daily (recurrent systemic thromboembolism with valve disease)
Dosing Considerations	Take with food	With or without meals; no dosage adjustment is necessary for elderly patients or patients with renal disease.	Take with food; May need to adjust dose in patients with renal impairment (monitor to determine)	With or without food; do not crush, chew, etc. the capsule	Take 1 hour prior to meals
Oral Dosage formulations	Tablets: 81, 325, 650 mg Enteric coated tablets: 81, 325, 975 mg Timed-release 800 mg tab	75 mg tablets	250 mg tablets	25/200 mg sustained-release capsules	25, 50, 75 mg tablets

B. Uses: The following table displays the uses of the antiplatelet agents according to The American Heart Association (AHA), American College of Cardiology (ACC), American College of Physicians/ American Society of Internal Medicine (ACP-ASIM) and The Sixth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy guidelines.

Disease State	ASA	Clopidogrel	Ticlopidine	ASA/DP-ER*	Dipyridamole
Primary Prevention of Cardiovascular Disease and Stroke	75-160 mg/day patients at high CHD risk; not if at risk for hemorrhagic stroke[8] Men > 50 yo with 1+ risk factor, ≥ 75 mg/day; Female > 50 yo with 1+ risk factor, no specific dose[9]	Only in ASA-intolerant or resistant patients[10] CHARISMA trial investigating clopidogrel/ASA as primary CAD prevention in high-risk patients[10]			

Disease State	ASA	Clopidogrel	Ticlopidine	ASA/DP-ER*	Dipyridamole
Primary Prevention of Ischemic Stroke[11]	75-150 mg/day				
Secondary Prevention of Ischemic Stroke	Recommended therapy; 50-325 mg/day[12,13]	Option to ASA;[12,13] Intolerant to ASA;[12] 75 mg/day MATCH trial investigation clopidogrel/ASA[14]	Option to ASA;[13] Option to clopidogrel or ASA/DP-ER;[13] 250 mg BID	Option to ASA;[13] Intolerant to ASA;[12] More effective than ASA[13]; 25/200 mg BID ESPRIT Trial investigation ongoing[15]	
TIA Management	Recommended therapy; 50-325 mg/day[12,13] North America consensus of 325 mg/day[16] Another regimen: 50-1300 mg/day[12]	Option to ASA;[12,13] Intolerant to ASA;[12] TIA while on ASA;[12] 75 mg/day MATCH trial investigating clopidogrel/ASA[14]	Option to ASA;[12,13] Option to clopidogrel[12,13] or ASA/DP-ER;[12] 250 mg BID	Option to ASA;[12,13] Intolerant to ASA;[12] TIA while on ASA;[12] 25/200 mg BID ESPRIT Trial investigating ongoing[15]	
Atherosclerotic Cardiovascular Disease[17]	75-325 mg/day; continue indefinitely	If ASA contraindicated; 75 mg/day			
Coronary Heart Disease	75-162.5 mg/day[9]	Contraindications to ASA: 75 mg/day[9] CHARISMA trial investigating clopidogrel/ASA[10]			
MI	160-325 mg/day; continue indefinitely[18]	Allergic or unresponsive to ASA[18]	Allergic or unresponsive to ASA[18]	No benefit over ASA[13]; Not recommended[9]	Allergic or unresponsive to ASA[18];

					Not recommended[9]
Atrial Fibrillation[19]	325 mg/day depending upon risk				
Chronic Stable Angina[20]	75-325 mg/day	Absolute contraindication to ASA; 75 mg/day	No decrease in CV adverse events		No benefit
Unstable Angina	75-325 mg/day; continue indefinitely[21]; 75-162.5 mg/day[9]	Unable to tolerate ASA[9,21]; Combine with ASA for up to 9 months;[21] 75 mg/day	Alternative to clopidogrel[21]; Unable to tolerate ASA[9] 250 mg BID		No benefit

Disease State	ASA	Clopidogrel	Ticlopidine	ASA/DP-ER*	Dipyridamole
Percutaneous Coronary Intervention	80-325 mg/day; continue indefinitely[22]	ASA intolerance; Adjunct to ASA in stent implantation;[21,22] 75 mg/day	ASA intolerance; Adjunct to ASA in stent implantation;[9] 250 mg BID		Not an alternative to ASA[22]
Rheumatic Mitral Valve Disease[23]	80-100 mg/day	Contraindications to ASA: 75 mg/day		Contraindications to ASA; 250 mg BID	Contraindications to ASA; 400 mg/day
Mitral Valve Prolapse[23]	160-325 mg/day				
Bypass Grafts: Saphenous Vein[24]	325 mg/day continued indefinitely	Allergic to ASA; 75 mg/day			Did not enhance ASA effects
Bypass Grafts: Internal Mammary Artery [24]	Daily dose to be continued indefinitely				
Chronic Extremity Arterial Insufficiency	81-325 mg/day[25]; 75-150 mg/day[26,27]	May provide better efficacy than ASA; 75 mg/day[25]			Addition to ASA may provide additional benefit[25]
Peripheral Vascular Reconstructive Surgery[25]	81-325 mg/day	Unable to take ASA; 75 mg/day			Addition of 75 mg TID to ASA may provide additional benefit
Mechanical Prosthetic Heart Valves[28]	80-100 mg/day				
Bioprosthetic Heart Valves[28]	80 mg/day				

* ASA/DP-ER = ASA plus dipyridamole-extended release formulation

C. Aspirin:

The following is additional information related to ASA:

- The Antiplatelet Trialist's Collaboration project, a meta-analysis of clinical trials evaluating antiplatelet therapy (up to September 1997), concluded the following:[26]

  Antiplatelet therapy should be considered for most all patients with suspected acute MI, unstable angina, or a history of MI, angina, stroke, TIA, arterial bypass surgery or angioplasty. Medium dose ASA (75-325 mg/day) is most widely tested antiplatelet regimen and the first choice in long-term prevention of cardiovascular events (e.g., MI, stroke, death).

- Results of a survey reported most responders (81%) consider ASA effective in improving outcomes in asymptomatic patients (> 65 years of age). In addition, ASA was considered beneficial in patients experiencing TIA (96%) or stroke (89%). Fewer individuals responded that other non-ASA antiplatelet agents were always/often effective for improving outcomes in patients without symptoms (27%), with TIA (47%), or with stroke (52%). Responders (n = 183) were a diverse group of providers (e.g., general internists [n = 80], neurologists [n = 16], vascular surgeons [n = 20]) from five VA medical centers.[29]

D. Clopidogrel (Plavix®, Bristol-Myers Squibb/Sanofi)

Clinical Trials: An overview of pivotal clinical trials evaluating clopidogrel is presented below.

Non-PCI/Coronary Intervention Trials

The CAPRIE trial was designed to directly compare clopidogrel with ASA to determine the difference in reducing the risk of a composite outcome cluster that consisted of ischemic stroke, MI, or vascular death.[30] The primary analysis of efficacy used the intention-to-treat principle and was based on the incidence of the first occurrence of ischemic stroke, MI, or vascular death. Patients with an established diagnosis of ischemic stroke, MI, or symptomatic atherosclerotic peripheral arterial disease were enrolled in this double-blind trial. Patients were randomized to receive either clopidogrel 75 mg (n = 9599) or ASA 325 mg (n = 9586); both agents were taken once daily with breakfast. The mean age (SD) of the participants was 62.5 (11.1) years; the majority of the patients were male (72%) and white (95%). The mean duration of follow-up was 1.91 years; 21.2% of the study participants permanently discontinued the trial study. The incidence of the primary endpoint was lower in the clopidogrel group compared to ASA (9.78% vs. 10.65%, respectively). The event rate per year was calculated to be 5.32% vs. 5.83%, respectively (RRR= 8.7%; 95% CI, 0.3 to 16.5; p = 0.0043). Based upon these results, the following numbers were calculated: RR: 0.92; ARR: 0.51%; RRR: 8.7%; NNT: 196 patients/year. Analysis of the PAD outcome event rate per year alone was the only statistically different comparison between clopidogrel and ASA (3.71% vs. 4.86%, respectively) (RRR = 23.8%, 95% CI, 8.9 to 36.2; p = 0.0028). Assessment of other events (e.g., vascular death alone, ischemic stroke, MI, amputation, or vascular death) resulted in non-statistically significant results between clopidogrel and ASA. The investigators concluded that clopidogrel is more effective than ASA in reducing the combined risk of ischemic stroke, MI, or vascular death in patients with atherosclerotic vascular disease. The overall safety profile of clopidogrel is at least as good as that of medium-dose ASA.

Primary side effects reported from the CAPRIE trial included rash (6.02% vs. 4.61% for clopidogrel and ASA, respectively) diarrhea (4.46% vs. 3.36%), GI disturbances (15.01% vs. 17.59%), and any bleeding episode (9.27% vs. 9.28%). Patients discontinued the study primarily due to rash (1.9% vs. 2.41%) and bleeding (1.2% vs. 1.37%). ASA was associated with a higher incidence of any reported GI hemorrhage (2.66% vs 1.99%), any severe GI hemorrhage (0.71% vs 0.49%), and study drug permanent discontinuation due to GI hemorrhage (0.93% vs 0.52%) than clopidogrel (all $p < 0.05$).[30]

Four post-hoc analyses were performed using the CAPRIE trial data. The first report evaluated the need for hospitalization for recurrent ischemia events and bleeding between the two groups.[31] Patients still taking or within 28 days of discontinuing therapy hospitalized due to angina, TIA, severe limb ischemia or bleeding were included in this analysis. Kaplan-Meier survival estimates over a 3 year period (average treatment duration of 3 years) were used. Less patients treated with clopidogrel were hospitalized for any ischemic or bleeding event (12.4% vs. 13.6%; RRR = 8.7%; p = 0.015). Individually, clopidogrel was associated with less ischemic events (10.9% vs. 11.8%; RRR = 7.7%; p = 0.48) and any bleeding event (1.8% vs. 2.2%; p = 0.59). No difference was reported between the two groups for the combined endpoint of all-cause death, all-cause stroke or MI (p = 0.113). Although, a variety of other endpoint combinations were statistically in favor of clopidogrel (all p < 0.02).

The CAPRIE investigators also conducted a post-hoc analysis assessing the reduction in recurrent ischemic events in patients with previous cardiac surgery.[32] A total of 1480 (7.75%) patients had a history of prior cardiac surgery; 775 of these received clopidogrel. Baseline patient demographics were similar in this subset of patients except for hypertension (64% vs 55% in the clopidogrel vs. ASA group, respectively; p < 0.001). The presence of risk factors (e.g., male gender, prior MI, angina, smoking) was higher in the patients with cardiac surgery history compared to the other patients in the CAPRIE trial (i.e., no cardiac surgery) (all p < 0.04). The composite primary endpoint from the CAPRIE trial was lower with clopidogrel (5.8% vs. 9.1% event rate per year; p = 0.004). Clopidogrel reduced the risk for the following individual outcome measures: vascular death (2% vs. 3.3%; p = 0.03) and MI (2.4% vs. 3.9%; p 0.037); no statistical difference was reported in all-cause mortality (2.6% vs. 3.4%) and stroke (2.6% vs. 3.5%). Clopidogrel also lowered the risk after combing outcome measures (e.g., death, MI, stroke, all-cause hospitalization). The investigators concluded that clopidogrel reduced the risk of ischemic events in this high-risk patient subgroup.

Another post-hoc analysis utilized the CAPRIE data to assess the effects of clopidogrel specifically in diabetics.[33] A total of 1914 and 1952 diabetics received clopidogrel and ASA, respectively. The primary endpoint event rate per year was lower in diabetics receiving clopidogrel than ASA (15.6% vs. 17.7%; p = 0.042). The prespecified primary outcome consisted of vascular death, all-cause stroke, MI or rehospitalization for ischemia or bleeding. Any bleeding event was the only individual event that was different between the two groups (1.8% vs. 2.8%; p = 0.31); there was no difference between the groups for the individual ischemic events and ischemic events added together as a group.

The investigators furthermore used the CAPRIE data to predict which patients are at a higher risk for MI.[34] Patient baseline data plus the occurrence of MI were assessed. Based upon a total of 617 patients experiencing an MI during the CAPRIE trial, Kaplan-Meier MI event rate during follow-up (1 to 3 years) was 5.04% vs. 4.2% in the clopidogrel vs. ASA groups, respectively (RRR = 19.2%; p = 0.008). The investigators also report a MI RRR of 1% to 30% for clopidogrel if 1 to 5+ risk factors are present.

Commentary: The results of the CAPRIE trial document a slight benefit of clopidogrel over ASA in reducing the composite endpoint of stroke, MI or vascular death. However no difference in the primary endpoint composite was measured in the clopidogrel versus ASA group for patients presenting with stroke at baseline for study inclusion (7.15% vs.

7.71%; p = 0.26); in addition, clopidogrel was associated with a slightly higher incidence of the primary composite endpoint in patients presenting with an MI (5.03% vs. 4.84%; p = 0.66). The investigators comment that the benefit of clopidogrel may not be identical across these three subgroups (p = 0.042 via test of heterogeneity).[30]

Although the results of this subgroup analysis report benefit with clopidogrel, a few issues need to be discussed. A few prerequisites should be present before subgroup analyses are conducted.[35] First, the clinical trial should be well-designed with sound methods. Subgroup analysis results from flawed studies may be of no importance. Second, the investigator may have conducted a multitude of subgroup analyses and only reported the statistically significant ones. As the number of statistical evaluations increase, the likelihood of finding a statistical difference by chance alone increases. Third, the power (ability to detect a difference) is reduced; results from a smaller number of study participants are analyzed compared to the entire study sample. Fourth, the overall study endpoint should be statistically significant before subgroup analyses are conducted. The CAPRIE trial was well designed and conducted plus the primary endpoint was statistically significant. The investigators do not discuss the number of subgroup analyses conducted, but the analysis by clinical subgroup (PAD, MI, stroke) is rationale since these are the individual components of the composite endpoint. However, the authors do later state that the study was not powered to detect a difference between the two groups based upon clinical subgroup. Thus the difference between the two groups in patients presenting with PAD may be due to chance.

In addition, the practice of designing and interpreting clinical trials that combine endpoints into a composite endpoint has been challenged.[36,37] Assessing the efficacy of a medication via combining clinical endpoints into one overall is common in the medical literature. A medication can reduce the risk of multiple adverse events (e.g., death, MI) and designing a study to measure the possible outcomes appears rationale. However, the readers of the results may be misled via the presentation and analysis methods. For instance, a medication should not be assumed to be beneficial for all endpoints measured with a statistically significant composite endpoint. If the composite endpoint consisted of three endpoints and one was reported being favorable, the other two endpoints can not be claimed beneficial individually. Statistical analysis needs to be considered in this situation since the study may have been designed with a lower sample size or shorter duration of follow-up based upon the composite, not individual, endpoints. These may occur due to a minimal number of subjects may be needed for the composite endpoint power analysis, while a larger sample usually is needed for the individual components of the composite endpoint.[36,37] In addition, the endpoints selected should be justified and the use of clinician-driven outcomes (e.g., hospitalizations, revascularizations) should not be included in the primary endpoint.[36]

Although the results of the post-hoc analyses of the CAPRIE trial report benefit with clopidogrel, a few issues need to be discussed. First, post-hoc analysis is a procedure to evaluate data for an outcome that was not pre-specified before the data were collected. This analysis identifies previously unrecognized findings or associations and the results cannot be used as evidence.[38,39] Limitations to this type of data evaluation include: selective data inclusion; confounding factors included either inadvertently or unknowingly; error or omission in measuring post-hoc outcome of interest during the trial; and inappropriate extrapolations.[38] This study design has been identified as a potential limitation for the results of these post-hoc trials.

Limitations to the rehospitalization CAPRIE post-hoc analysis include: Not all patients randomized in the CAPRIE trial were included; adverse events were not adjudicated by a clinical events committee; length of stay data were not recorded; types of hospitalization procedures were not complete; criteria classifying existing hospitalization stay being extended was subjective.[31] Also, re-hospitalization can be considered an investigator-driven outcome; these types of outcomes have been suggested to influence statistical significance and more amendable to change (i.e., investigator option) instead of a specific definition.[36]

In addition, factors should be considered before applying the results of the post-hoc analysis in patients with prior cardiovascular surgery.[40-42] These include the mean age of the bypass graft was not determined; the exact type of cardiac operative procedure and type of graft (venous or arterial) were not identified; and the patients enrolled in the CAPRIE study may have been higher-risk patient than the typical cardiac surgery patient.[32,40] Furthermore, the investigators state in a latter correspondence that: 1. "[F]urther study is necessary to define the optimal antiplatelet regimen for secondary prevention in patients who have undergone CABG." 2."[Q]uestions remain about the exact role of clopidogrel in the subset of patients who underwent CABG…". 3. "[W]e reiterate that a dedicated randomized clinical trial of clopidogrel plus aspirin versus aspirin alone (or clopidogrel alone) after CBG performed for a range of elective and urgent indications is warranted."[41]

Although clopidogrel lowered the primary endpoint in diabetics, various aspects of this analysis need to be identified. No consistent definition of diabetes was used by each investigator; plus no specific laboratory confirmed the diagnosis. Also, the severity and duration of diabetes was not known. In addition, information addressing diabetes control was not available. Furthermore, the primary endpoint of this analysis was not exact as the CAPRIE trial; any bleeding event was added, which "tipped" the results to be significant in this post-hoc assessment.

Furthermore the investigators concluded that the analysis favors clopidogrel for patients at risk of developing an MI, the previously mentioned study limitations of post-hoc analysis apply to this report. In addition, the results of this report were based upon only 617 (3.22%) patients that were included in the entire CAPRIE study.

The results of the CAPRIE trial do provide evidence that clopidogrel is a useful antiplatelet agent for secondary cardiovascular prevention. Although, the results of this study (as a whole, via subgroup analysis or post-hoc analysis) do not automatically indicate clopidogrel to be the antiplatelet agent of choice over ASA in all patients. The modest reduction of the composite endpoint (RRR = 8.7% but an ARR of only 0.51% and NNT of 196 patients/year) needs to be considered in conjunction with the adverse effects plus monthly drug cost. National guidelines recommend ASA for initial therapy in patients with atherosclerotic cardiovascular disease, chronic stable angina, or MI and for secondary stroke/TIA prophylaxis.[9,12,13,17,18,20,43] Clopidogrel is considered alternative therapy for most of these patients or if a patient has ASA intolerance/contraindications. Besides these publications, additional publications recommend ASA over clopidogrel, unless the patient is resistant[10] (5-10% of patients with stable cardiovascular disease) or intolerant/contraindications to ASA.[9,10,43-51]

Furthermore, results from a cost-effectiveness analysis do not favor clopidogrel for all eligible patients. Four antiplatelet regimens were assessed for secondary prevention in patients >35 years of age with

coronary disease.[52] The estimated incremental cost per quality-adjusted year of life gained increases from $11,000 to $250,000 by converting all eligible patients from ASA to clopidogrel. However, prescribing clopidogrel for all patients plus combining ASA (for patients not allergic to ASA) changes the cost to $130,000. Some patients are hypersensitive to ASA and clopidogrel is an alternative; the cost in this group increases to $32,000 (ASA for all eligible patients and clopidogrel for ASA-sensitive patients). The investigators concluded that increasing ASA use as a coronary heart disease secondary prevention method is cost-effective. Also, clopidogrel should be reserved for patients unable to take ASA (from a cost-effective perspective). The results of this analysis have been endorsed by other practitioners.[51,53-56]

PCI/Coronary Intervention Trials

The CURE trial documented a reduced risk of MI and recurrent ischemia with the combination of clopidogrel plus ASA in patients with ACS and no ST-segment elevation.[57] These patients were randomized to double-blind therapy of either placebo LD (n = 6303) or clopidogrel (300 mg LD, then 75 mg once daily; n = 6259) for 3 to 12 months (mean duration, 9 months). All patients also received ASA (75 to 325 mg once daily). The first primary endpoint was the composite of death from cardiovascular causes, nonfatal MI, or stroke; the second primary endpoint was the composite of the first primary endpoint or refractory ischemia. The average (SD) age of the study participants was 64 (11.3) years and 61% were male; mean time from pain onset to randomization was 14 hours. The incidence of the first primary endpoint was lower in the clopidogrel group compared to placebo (9.3% vs 11.4%, respectively; RR = 0.8; 95% CI, 0.72-0.9; $p < 0.001$). Similar results were measured with the second primary endpoint (16.5% vs 18.8%, respectively; RR = 0.86; 95% CI, 0.79-0.94; $p < 0.001$). No difference was reported for most all individual outcomes (e.g., stroke, refractory ischemia, cardiovascular death). Baseline medication use did not confound the results between the two groups.

The primary adverse effect reported in the CURE trial was bleeding. Major bleeding episodes occurred more in the clopidogrel group than with placebo (3.7% vs 2.7%; RR = 1.38; 95% CI, 1.13-1.67; $p = 0.001$). Also more major bleeding episodes were higher with clopidogrel within 30 days (2% vs. 1.5%) and >30 days (1.7% vs. 1.1%) of study enrollment. Minor bleeding also was higher with clopidogrel (5.1% vs 2.4%; $p < 0.001$). In addition, more transfusions of ≥ 2 units of blood was required with clopidogrel (2.8% vs 2.2%; $p = 0.02$). Although numerically higher with clopidogrel, no statistical difference was reported between the two groups in terms of life-threatening or fatal bleeding episodes, bleeding requiring surgical intervention, hemorrhagic stroke, thrombocytopenia or neutropenia. Major bleeding within 7 days was higher in patients stopping clopidogrel therapy ≤ 5 days (9.6%) than ≥ 5 days (4.4%) of CABG surgery.[57]

The PCI-CURE trial documented that administering clopidogrel plus ASA reduced the risk of major ischemic events after PCI compared to ASA alone.[58] The results of the CURE trial were analyzed specifically in those patients undergoing PCI and treated with clopidogrel/aspirin (n = 1313) or placebo (n = 1345). After PCI, >80% of all patients received ASA combined with either clopidogrel or ticlopidine. According to the intention-to-treat analysis, fewer patients treated with clopidogrel LD plus ASA experienced cardiovascular death, MI, or urgent revascularization within 30 days after the procedure compared to placebo (4.5% vs 6.4%, respectively; RR = 0.70; 95% CI, 0.50-0.97; $p = 0.03$). Most all subgroups (e.g., men, non-diabetics, age ≤ 65 years) had a lower

incidence of adverse events with clopidogrel. Major bleeding complications occurred in ~1.5% of the patients (p = 0.69) from PCI to 30 days.

One-year follow-up data for the CURE trial recently has been published.[59] According to these results, clopidogrel continues to reduce the incidence of the combined endpoint of cardiovascular death, MI or stroke compared to placebo. Overall (1 year data), less people in the clopidogrel group experienced the primary endpoint than placebo group (10.6% vs 12.5%; RR = 0.84; 95% CI, 0.76-0.93). In addition, similar results were reported after analysis of the data from days 31 to 1 year (5.2% vs 6.3%; RR = 0.82; 95% CI, 0.7-0.95). Major bleeding occurred in 1.75% and 1.18% in the clopidogrel and placebo, respectively over a mean of 8 months (RR = 1.48; 95% CI, 101 to 1099).

After the PCI-CURE study, questions still remained regarding clopidogrel therapy in patients undergoing a PCI procedure.[60] For instance, these patients were a subgroup of the CURE trial. Also, this trial was an observational study and patients received open-label thienopyridine (either clopidogrel or ticlopidine). In addition, the time of PCI varied between 3-106 days; median time before PCI was 6 days during initial hospitalization and 10 days for all patients (i.e., during hospitalization or after discharge). Furthermore, the optimal duration of therapy was still undetermined. Thus, the CREDO trial[61] was conducted to answer some remaining questions.

This trial reported that continuing clopidogrel (in combination with ASA) after elective PCI for at least 1 year reduces the risk for major thrombotic events.[61] Patients with symptomatic CAD with objective evidence of ischemia, referred for PCI, or high likelihood for requiring PCI were enrolled. The primary endpoint was the composite of death, MI, and stroke at 12 months (intention-to-treat) and the composite of death, MI, or urgent revascularization at 28 days (per-protocol). Secondary endpoints included individual components of primary endpoint (e.g., death alone, MI alone); endpoints with clopidogrel administration < 6 hours or $\geq$ 6 hours prior PCI; revascularization in target vessel or any revascularization at 12 months; and bleeding (minor, major, insignificant). Patients were randomized to double-blind treatment of either clopidogrel 300 mg LD (n = 1053) or placebo LD (n = 1063) 3-24 hours prior PCI; all received ASA 325 mg once daily. All patients received clopidogrel 75 mg once daily and ASA 325 mg once daily for 28 days after PCI. At day 29, patients receiving 300 mg clopidogrel prior PCI continued taking clopidogrel 75 mg once daily. Patient taking placebo prior PCI took placebo. Aspirin 81-325 mg once daily continued at the discretion of investigator. Approximately 51% of the patients had clopidogrel LD 3 to <6 hours prior PCI; 49% received the LD 6-24 hours prior PCI. The mean duration between study drug LD and PCI was 9.8 hours. Approximately 62% of the patients in both groups completed the 1-year study. At day 28, there was no difference in the primary endpoint among the pretreatment groups: 6.8% vs 8.3% in clopidogrel vs placebo, respectively (p = 0.23). However, patients receiving clopidogrel LD at least 6 hours prior to PCI had reduction in endpoint incidence (although p = 0.051). After 1 year, the incidence of the primary endpoint was lower with clopidogrel: 8.5% vs 11.5% (RRR = 27%; 95% CI, 3.9-44.4%; p = 0.02). No significant increase in bleeding occurred with clopidogrel LD at day 28. There was a trend toward increased major bleeding with clopidogrel compared to placebo at 1 year (8.8% vs 6.7%, p = 0.07).

No differences in major bleeding episodes were reported between clopidogrel and placebo groups in the CREDO trial after 1-year (8.8% vs 6.7%; p = 0.07). Similar episodes of minor bleeding were reported between the two groups (5.3%

vs 5.6%; p 0.84). No differences in major or minor bleeding between the two groups at day 28 was reported (both p > 0.2).[61]

The PRONTO trial evaluated the effects of clopidogrel LD in patients undergoing elective stent placement without glycoprotein (GP) IIb/IIIa receptor antagonists.[62] A total of 100 patients were equally divided to receive one of four different clopidogrel loading regimens: 300 mg 24 hours before (Group A); 12 hours before (Group B); 3 to 6 hours before (Group C); or 75 mg at the time of intervention (Group D). All four groups received a 75 mg dose and ASA 325 mg at the time of procedure; ASA ≥ 81 mg daily was administered for 1 week prior the procedure and ASA 325 mg daily afterwards for at least 30 days. Clopidogrel effects were measured by blood sample tests (platelet aggregation, ADP-induced aggregation, shear-induced closure time, GP IIb/IIIa expression). These results indicate that the 300 mg clopidogrel LD should be administered 3 to 24 hours before stenting to inhibit platelets at the time of the procedure and reduce post-stent activity instead of the 75 mg dose given at the time of the procedure. No cases of 30-day repeat target vessel revascularization, Q-wave MI, stroke or death occurred, although only 100 patients were enrolled.

Results from the above trials document a reduction in adverse events in patients with ACS treated with the combination of clopidogrel plus ASA compared to ASA. A difference in reducing adverse event outcomes was reported as early as 24 hours after therapy was initiated. Based upon the CURE results, 48 and 43 patients needed to be treated with clopidogrel/ASA to prevent one first and second primary endpoint event, respectively. The combination of clopidogrel plus ASA also reduces the risk of adverse events over a duration of at least 1 year in patients undergoing PCI. However, the clopidogrel loading dose should be administered at least 6 hours before the procedure.[61] Bleeding rates are higher with the combination, but this higher risk appears to be outweighed by the reduction in morbidity and/or mortality. The risk of bleeding with the combination regimen being higher than ASA alone continues throughout therapy (up to 1 year). In addition, the studies only evaluated the use of this combination for up to 12 months. Based upon the differences in mechanism of action between clopidogrel and ASA plus the recommendation for indefinite ASA therapy in these patients, continuing combination therapy beyond 1 year appears theoretically advantageous. However, clinical trials should be conducted to provide evidence to answer this question (specifically extended duration of use > 1 year).

The ACC/AHA unstable angina and non-ST-segment elevation MI management guideline recognizes clopidogrel as a class I agent in patients unable to take ASA (contraindication or GI intolerance). Clopidogrel in combination with ASA also should be given to hospitalized patients for whom an early non-interventional approach is planned. Administer these two drugs as soon as possible and continue for at least one month. In addition, clopidogrel should be started before PCI and continued for at least one month. Ticlopidine is not preferred in patients with unstable angina since clopidogrel has a faster onset of action and better safety profile. Aspirin is to be administered as soon as possible after presentation and continue indefinitely (75 to 325 mg/day). All procedures to treat unstable angina include the use of ASA.[21]

Heart Failure and Atrial Fibrillation Trials

The use of clopidogrel plus ASA in patients with heart failure (HF) for stroke prevention is being investigated. Results of two preliminary studies suggest that this combination

may not be better than warfarin. These studies enrolled a small sample size (n = 20; n = 70) and measured surrogate endpoints (e.g., plasma markers of thrombogenesis or platelet activation, but not incidence of stroke, MI, death).[63,64] Results of a small study (n = 43) report that clopidogrel (75 mg once daily for 8 days) administered to patients with non-valvular atrial fibrillation does not affect stabilized warfarin therapy.[65] Two large studies are being conducted (Warfarin and Antiplatelet Therapy in Chronic Heart Failure [WATCH][66-68] and Plavix Use for Treatment of Congestive Heart Failure [PLUTO-CHF][64]) that will assess the use of clopidogrel in patients with HF. Until these study results become available, routine use of clopidogrel in this patient type can not be recommended.

Other Clopidogrel Studies

Clopidogrel has been compared to ASA in patients undergoing mechanical aortic valve replacement.[69] Exclusion criteria included patients with atrial fibrillation or LVEF < 35%. Patients were randomized to open-label therapy of either clopidogrel plus ASA (n = 11) or phenprocoumon (n = 11). The study was stopped prematurely after one patient receiving clopidogrel plus ASA developed an aortic valve thrombosis. The investigators, although only enrolling a very small number of patients, concluded this drug combination was not useful for this cardiac procedure.

F. Aspirin/Sustained-Release Dipyridamole (Aggrenox®, Boehringer Ingelheim)

Clinical Trials: An overview of the clinical trial evaluating ASA/extended-release dipyridamole is presented below.

The European Stroke Prevention Study-2 (ESPS-2) evaluated four treatment groups that included ASA (25 mg BID), modified-release dipyridamole (DP, 200 mg BID), the combination of both agents (25/200 mg BID), and placebo in determining the safety and efficacy and safety of these agents in the secondary prevention of ischemic stroke.[70] Three outcomes were measured over two years as primary endpoints: stroke; death; stroke and/or death. A total of 6,602 patients with previous history of TIA or ischemic stroke within the previous three months were equally randomized to one of the four groups in this double-blind trial. The mean age of the study participants was 66.7 years; 58% were men and ischemic stroke occurred in 76% of the patients. The incidence of stroke was lower in patients taking the combination than ASA alone, dipyridamole alone, or placebo (9.52% vs 12.49%, 12.76% and 15.15%, respectively; $p < 0.01$). The incidence of TIA was lower with the combination also (10.55% vs 12.63%, 13.21% and 16.46%, respectively). The combination therapy had a slightly lower rate of death or strokes compared to the other therapies (17.33% vs 20.01%, 9.41%, and 22.92%, respectively; $p > 0.05$). However, ASA had a higher 24-month survival than the combination (89.06% vs 88.76%). There was no difference among the groups in regard to MI. The investigators concluded that the combination was an efficacious therapy for secondary prevention of stroke and TIA.

The primary side effects reported in the ESPS-2 trial included bleeding from any site (8.73% vs 8.19% for ASA/DP vs ASA, respectively), headache (33% vs. 38%), and dizziness (29% for both groups). Approximately 31% of patients in these two groups reported at least one GI side effect (e.g., diarrhea, nausea). More people discontinued

the combination therapy due to a GI event (7.03% vs 3.7%) and headache (8.06% vs 1.88%) compared to ASA, respectively.[70]

Commentary: The ESPS-1 study documented dipyridamole (non-sustained release preparation) plus ASA reduced the relative risk of stroke by 38% compared to placebo in patients with a recent cerebrovascular event of atherothrombotic origin (TIA, reversible ischemic neurological deficit, or stroke). This randomized double-blind study evaluated dipyridamole and ASA (75 mg and 325 mg, respectively, both dosed TID; n = 1250) to placebo (n = 1250) for 2 years. The primary endpoint (stroke or death from any cause) and death rates were lower in the combination group than placebo (15.2% vs. 22.6%, $p < 0.001$ and 8.6% vs. 12.5%; $p < 0.01$).[71]

The results of the ESPS-1 study are limited since the combination was only compared to placebo and no active comparative group was included (i.e., ASA alone). The benefit of adding dipyridamole to ASA this can not be accurately assessed, especially since other studies do not consistently report an additional reduction in adverse events with dipyridamole-immediate release plus ASA.[49,72] The ESPS-2 study concludes a greater benefit of dipyridamole-ER plus ASA than either agent individually or placebo. Although, a few factors need to be considered. ASA compliance was 87% versus 97% for the dipyridamole-ASA combination. This study evaluated a low-dose ASA regimen (50 mg/day). A debate has been in the literature regarding the lowest effective daily ASA dose for stroke prevention. Most of the argument is between 81 mg versus 325 mg per day.[48,49,73-76] Most all published recommendations and other publications recommend ASA at a daily dose of at least 75 mg.[17,16,26,43,51,73,74,76] Thus even though the ESPS-2 study reported the dipyridamole-ER/ASA combination to be more effective than ASA alone, the study design may have be a reason for this outcome. In addition, other reasons that include chance, improved bioavailability of the dipyridamole formulation, and blood pressure lowering effect by dipyridamole could be the reasons for the improved outcome over ASA.[26]

G. Ticlopidine (Ticlid®, Roche)

Clinical Trials: An overview of the primary clinical trials evaluating ticlopidine is presented below:

The CATS trial documented the antiplatelet activity of ticlopidine.[77] Patients were randomized to either ticlopidine (250 mg twice daily) or placebo for a mean of 2 years. The incidence of subsequent stroke, MI, or vascular death in patients with a recent thromboembolic stroke the endpoint was lower with ticlopidine (10.8% vs. 15.3%, $p = 0.006$). Reversible severe neutropenia occurred in ~1% of the patients.

The TASS trial also documented the anti-platelet activity of ticlopidine, but was compared to ASA. Patients with recent transient or mild persistent focal cerebral or retinal ischemia were randomized to either ticlopidine (250 mg BID; n = 1529) or ASA (650 mg BID; n = 1540).[78] Nonfatal stroke or death from any cause during the follow-up period was lower with ticlopidine (20% vs. 22.7%). Reversible severe neutropenia was reported in < 1% of the patients.

A subgroup analysis of African-Americans enrolled in TASS reported a 24% relative risk reduction for stroke and death with ticlopidine compared to ASA (specific numbers not provided in study). Since this population has a high prevalence of stroke, the findings of

this subgroup analysis lead to the design and implementation of the African American Antiplatelet Stroke Prevention Study (AAASPS), which specifically compared ticlopidine to ASA and enrolled only African American patients.[79,80] Patients with non-cardioembolic ischemic stroke with onset between 7 and 90 days were enrolled; no patients with TIA were included. Patients were randomized to double-blind therapy of either ticlopidine (250 mg BID; n = 902) or ASA (325 mg BID; n = 907) for 2 years. Average follow-up data was 1.54 years per patients; median follow-up was ~714 days. Median medication compliance was 91% for both groups; only 41% and 44% of ticlopidine- and ASA-treated patients completed 2 years of study. The incidence of composite endpoint of recurrent stroke, MI, or vascular death was greater in patients taking ticlopidine (133 [14.8%] vs. 112 [12.4%]; p = 0.12). No difference was measured between the two groups via intention-to-treat and per-protocol analyses. No differences for other outcome measures (e.g., stroke type or severity, MI alone, recurrent stroke). Ticlopidine was associated with severe reversible neutropenia (< 1%), rash (14%) and thrombocytopenia (0.3%).

As reported in the trials listed above, severe (but reversible) neutropenia occurred in ~1% of the patients. In addition, rash was commonly reported in patients taking ticlopidine.[77,78,80] Blood tests are to be conducted in patients taking ticlopidine to monitor for neutropenia.[3] After the introduction of clopidogrel, ticlopidine was no longer considered an alternative to ASA since clopidogrel is not associated with neutropenia. Ticlopidine is still marketed and prescribed; due to the safety concerns, national guidelines refer this agent to be an alternative to clopidogrel.

According to the package labeling of ticlopidine, the following monitoring parameters are recommended:[3]

- CBC's including platelet count and leukocyte differential prior to initiation of therapy and every two weeks until the end of the third month of therapy.
- More frequent monitoring and post-third month monitoring should be done for patients with clinical manifestations that suggest adverse hematologic effects.

H. Non-ASA Comparative Studies: Clinical trials have directly compared clopidogrel to ticlopidine; however, these are in patients receiving coronary stents.

One of the first published study to directly compare clopidogrel to ticlopidine in patients who underwent coronary stenting was designed as a prospective cohort trial.[81] During a 30 month period, patients (n = 1406) received ticlopidine (500 mg LD followed by 250 mg BID for 2 weeks); the next 4 months, patients (n = 283) received clopidogrel (300 mg LD followed by 75 mg once daily for 4 weeks). All patients received ASA 325 mg once daily. No differences were present in the patient demographics; there was only one difference in the procedure (minimum lumen diameter; p = 0.02). The incidence of stent thrombosis (1.54% vs 1.5%; p = 1.0) or major adverse cardiac events (2.4 vs 3.1%; p = 0.85) were similar between the two groups, respectively. However, the incidence of specific side effects (neutropenia, diarrhea, rash) was greater in the ticlopidine group (10.6% vs 5.3%; RR = 0.53; CI, 0.32-0.86; p = 0.006).

Another cohort study compared the safety and efficacy of ticlopidine with clopidogrel in patients receiving coronary stents.[82] The 30-day event rates were compared between 500 consecutive coronary stent patients treated with ASA and clopidogrel (300 mg LD immediately prior to stent placement, and 75 mg/day for 14 days) to 827 consecutive stent

patients treated with ASA and ticlopidine (500 mg LD and 250 mg twice daily for 14 days). No difference was reported between the clopidogrel and ticlopidine in terms of mortality (0.4% vs 1.1%), nonfatal MI (0% vs 0.5%), stent thrombosis (0.2% vs 0.7%), bypass surgery or repeat angioplasty (0.4% vs 0.5%) and any event (0.8% vs 1.6%) (p = NS for all comparisons).

Results of a direct comparative study suggest no difference between clopidogrel and ticlopidine after coronary artery stent placement.[85] Patients were randomized to open-label therapy of either ticlopidine (250 mg BID; n = 345) or clopidogrel (75 mg once daily; n = 355) for 4 weeks. Each patient also received ASA 100 mg once daily. Therapy was started immediately after the procedure. No differences were present in regards to patient demographics and procedures. The incidence was similar between the ticlopidine and clopidogrel (1.7% vs. 3.1%; p = 0.24) for the primary cardiac endpoint (cardiac death, urgent target vessel revascularization, angiographically documented thrombotic stent occlusions, or nonfatal MI within 30 days). The primary noncardiac endpoint (e.g., noncardiac death, hemorrhagic complication) occurred less in the clopidogrel group (9.6% vs. 4.5%, respectively; p = 0.01).

The investigators also conducted a follow-up to the above study.[86] The median time of follow-up from randomization to last patient contact or death was 28 and 27 months for ticlopidine and clopidogrel, respectively. The primary endpoint (cardiovascular death during entire follow-up) was lower with ticlopidine than clopidogrel (8 vs. 26 patients). The combined end point of cardiovascular death or nonfatal MI also was lower with ticlopidine (19 vs. 40 patients, respectively; p = 0.005).

A prospective study evaluated the safety of clopidogrel compared to ticlopidine in European patients undergoing stent placement.[87] The primary end point was measured as major peripheral or bleeding complications, neutropenia, thrombocytopenia, or early discontinuation of study drug as the result of a noncardiac adverse event. Patients were randomized to double-blind therapy of either (1) clopidogrel 300 mg LD plus ASA 325 mg on day 1, followed by clopidogrel 75 mg once daily (n = 345); (2) clopidogrel 75 mg once daily (n = 335); or (3) ticlopidine 250 mg BID (n = 340). All three groups also received ASA 325 mg daily; drug therapy was started within 6 hours after the procedure. Therapy was continued for 28 days. No difference was reported for patient baseline demographics and stent procedures. The incidence of the primary endpoint was higher in the ticlopidine group compared to the combined clopidogrel groups (9.1% vs 4.6%; RR = 0.5; 95% CI, 0.31-0.81; p = 0.005). In addition, the primary endpoint was lower with the clopidogrel LD compared to no LD (2.9% vs. 6.3%; p = 0.043). Although the study was not powered to detect differences between the regimens in terms of major adverse clinical events, the two clopidogrel groups had a higher incidence than ticlopidine (1.2% [LD] and 1.5% [no LD] vs. 0.9%, respectively; p = NS).

A meta-analysis was conducted to determine if clopidogrel is at least as efficacious as ticlopidine after coronary stent procedures.[89] The primary endpoint of this analysis was the 30-day major adverse cardiac events (MACE), as defined in each trial, rate. A total of 13,955 patients were enrolled in the included trials. The pooled rate of MACE was lower with clopidogrel than ticlopidine (2.10% vs. 4.04%, respectively). Clopidogrel also lowered the ischemic event rates (OR = 0.72; 95% CI, 0.59-0.89, p = 0.002 after adjustment for heterogeneity in the trials) and mortality (-0.48% vs. 1.09%; OR = 0.55, 95% CI, 0.37-0.82;

p = 0.003). The authors concluded that clopidogrel is at least as efficacious as ticlopidine in reducing MACE plus better tolerated and lower incidence of side effects.

The above studies do not include a placebo or ASA arm since previous studies with ticlopidine plus ASA documented a greater reduction in the adverse events compared to ASA +/- warfarin.[90,91] As a whole, the results of the above studies at times are conflicting; some favor ticlopidine, while other favor clopidogrel. A few study design characteristics need to be identified. Not all include these, but the following should be considered in assessing these trials: no LD prior the procedure; therapy started after the procedure; and non-randomized or open-labeled; primary endpoint differences; lack of power analysis included in the methods (i.e., sample size may not have been sufficient to measure mortality differences between two drugs); differences in stenting procedures between North America and European countries; and duration of antiplatelet therapy. The conclusions of these studies do indicate that the combination of ASA plus either ticlopidine or clopidogrel reduce adverse events after stenting procedures.

I. Antiplatelet Clinical Trials in Progress:

MATCH Trial (Management of Atherothrombosis with Clopidogrel in High-risk Patients with Recent Transient
Ischaemic Attack or Ischaemic Stroke): The efficacy and safety of clopidogrel plus ASA versus clopidogrel alone in patients with recent TIA or ischemic stroke and with at least one additional risk factor.[14,68] Approximately 7,600 patients will be enrolled, with treatment and follow-up for each patient lasting 18 months. The primary combined efficacy endpoint will be the first occurrence of an event in the composite of ischemic stroke, MI, vascular death or rehospitalization for an acute ischemic event during the follow-up period.[14]

ISAR-REACT Trial (Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment):[93] Patients who had symptoms of CAD and scheduled to undergo coronary angiography. These patients are extremely unlikely to require CABG within days of angiography. They will receive a clopidogrel 600 mg loading dose at least 2 hours before the procedure. Patients will then be randomized to either abciximab and reduced dose heparin or standard dose heparin and placebo. The primary endpoint is the composite of death, MI, and urgent target vessel revascularization within 30 days.

ESPRIT Trial:[15] A study that will randomize patients with a TIA or minor ischemic stroke randomized to oral anticoagulation (INR 2.0-3.0), the combination of dipyridamole (400 mg daily) plus ASA (in any dose between 30-325 mg daily) or ASA only. The primary endpoint is the composite event death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding complication, whichever occurs first. A total of 4,500 patients from more than 10 countries are planned to be enrolled; the mean follow-up will be 3 years.

CHARISMA trial:[10] Combination of ASA plus clopidogrel to ASA alone for secondary prevention and high-risk primary prevention of CAD.

WATCH (Warfarin and ASA Therapy in Congestive Heart Failure): Warfarin versus clopidogrel versus ASA in patients with chronic heart failure to prevent thromboembolic complications.[66-68] Three groups will be compared for a minimum of 2 years: open-label warfarin; aspirin; or clopidogrel.[68]

PLUTO-CHF:[66] Assessing clopidogrel in patients with congestive heart failure.

COMMIT (Clopidogrel and Metoprolol in MI Trial):[68] Clopidogrel plus aspirin to aspirin alone in patients with suspected acute MI; usual therapy for acute MI (e.g., thrombolytic) will be administered. (AHJ April 2003)

INTERACTION:[94] Clopidogrel plus atorvastatin (drug-drug interaction study).

J. Safety: The following table displays a comparison of the package labeling safety issues among the anti-platelet agents.[1-4]

Safety Issue	Aspirin	Clopidogrel (Plavix®)	Dipyridamole/ASA (Aggrenox®)	Ticlopidine (Ticlid®)
Box Warning	N/A	N/A	N/A	Hematologic reactions, TTP*, Aplastic anemia, Neutropenia, Agranulocytosis
Contraindications	ASA allergy, Reye's syndrome	Active bleeding	ASA allergy, Reye's syndrome	Neutropenia, Active bleeding, Liver Impairment
Warnings	GI side effects, PUD, pH warning (as noted previously)	TTP* (rare)	Coagulation abnormalities, GI side effects, PUD, pH warning: ↑ pH causes low ASA serum levels, ↓ pH causes high ASA serum levels	Hematologic reactions, Neutropenia, TTP*, Aplastic anemia, Pancytopenia, Increased cholesterol
Precautions	Risk of bleeding, Ulcers, Hemorrhagic status, Angioedema, Nasal polyps associated with asthma, Thrombocytopenia	Increased bleeding possibilities, GI Bleeding, Hepatic Impairment	Coronary artery disease, Hepatic insufficiency, Decreased blood pressure, Renal failure, Risk of bleeding	Increased bleeding possibilities, GI bleeding, Hepatic impairment, Renal impairment, Liver disease

*TTP: Thrombotic Thrombocytopenic Purpura

K. Drug Interactions: The combination of warfarin in patients taking either ASA or clopidogrel is not an absolute contraindication. The patient should be monitored closely.[1,2,65,95] Patients should avoid taking ibuprofen with ASA since ibuprofen antagonizes the irreversible platelet inhibition induced by ASA. However, concomitant use of rofecoxib, acetaminophen, or diclofenac do not affect platelet inhibition by ASA.[96] NSAID use with clopidogrel should be monitored closely.[2,95] Corticosteroids may affect the antiplatelet activity of ASA.[1,95] The pharmacology of ACE inhibitors and sulfonylurea agents may be altered by ASA; monitor patient closely.[1,95] There is a debate regarding the significance of the ASA and ACE inhibitor interaction; based upon the available information, additional research is needed since some of the data was obtained from retrospective analyses. A small crossover study of 18 patients with chronic HF did report a mean

increase in mean VO_2max with clopidogrel compared to ASA (both in combination with an ACE inhibitor). However, mean exercise duration was not changed between the two groups.[98]

The results of a recently published study report that atorvastatin decreases the anti-platelet effects of clopidogrel.[100] In this prospective study, 44 patients received clopidogrel 300 mg as an oral loading dose (LD) followed by 75 mg daily for 28 days after coronary artery stent implantation. Before stent placement, patients received an eptifibatide LD (180 mcg/kg) followed by a continuous infusion (2 mcg/kg/min) for less than 12 hours. Statin use was not the same in all patients: 16 patients received no statin; 9 patients were taking pravastatin 40 mg daily; and 19 patients were taking atorvastatin daily (10 mg [n = 7], 20 mg [n = 7] or 40 mg [n = 5]). Platelet aggregation was measured before clopidogrel administration and 24 hours later in all patients. Measurements were repeated 6 to 8 days after stent implantation in patients receiving clopidogrel alone and in patients taking clopidogrel plus the statin. The in-vivo effects after 24 hours are as follows: administration of clopidogrel alone reduced mean platelet aggregation from 92% to 34% ($p < 0.0001$ from baseline); clopidogrel co-administered with pravastatin reduced mean platelet aggregation from 93% to 46% ($p < 0.0001$ from baseline). Atorvastatin 10 to 40 mg co-administered with clopidogrel reduced mean platelet aggregation only from 93% to 77% (p = NS from baseline). After 6 to 8 days, atorvastatin produced a dose-dependent effect on clopidogrel platelet aggregation: no atorvastatin, 34% platelet aggregation; atorvastatin 10 mg, 58% ($p = 0.27$); 20 mg, 74% ($p = 0.002$); and 40 mg, 89% ($p = 0.001$). Prudent options for patients in which clopidogrel is initiated include starting atorvastatin at a low dose or administering pravastatin, which is not metabolized by the CYP3A4 enzyme.

The change in antiplatelet effect of clopidogrel by atorvastatin may be explained by atorvastatin inhibiting CYP450, which is required to convert the prodrug clopidogrel to the active form. Even though this study reported an interaction between atorvastatin and clopidogrel, the clinical affect of this interaction was not assessed in this study. Since many patients most likely are taking both atorvastatin and clopidogrel, reduction in thrombosis risk and inflammation by statins may compensate for this interaction. Although not studied, other CYP450 3A4 inhibitors (e.g., lovastatin, simvastatin) may inhibit clopidogrel activation, thus reducing the antiplatelet activity of clopidogrel. Further research is needed to determine the overall clinical affects of the statin-clopidogrel interaction.[100]

After the publication of the interaction report, additional information has been published discussing this interaction.[94,101] One report challenged the interaction significance by identifying various factors not addressed in the drug-drug interaction report. These included a small sample size; retrospective, non-randomized analysis; poorly defined patient selection criteria; and lack of control regarding the other medications inhibiting CYP 450 taken by the study subjects. Also, clopidogrel is metabolized by more than one cytochrome P450 (CYP450) isoenzyme, and more than one test is available to measure platelet activity; plus previous pivotal clopidogrel studies (CAPRIE and CURE) enrolled patients taking a statin. In addition, results of the INTERACTION study, which is currently evaluating the clopidogrel and atorvastatin interaction, are not available.[94] Furthermore, a limited number of tests (in vitro point-of-care MICROS cell counter and the Plateletworks test) were used to assess platelet function in patients taking this drug combination. Multiple tests should be used to evaluate this drug-drug interaction.[101,102] Thus until further data are

available, these two drugs in combination should be prescribed to patients in which these drugs are indicated.[94]

Results of subgroup analysis of studies evaluating a COX-2 inhibitor suggest the combination of low-dose ASA (≤ 325 mg/day) with the COX-2 inhibitor may increase the incidence of GI ulcers.[103] However since these are subgroup analyses, limitations to this type of analysis (e.g., small sample size) need to be considered. Further research is required to quantify the extent of GI ulcer development in patients taking low-dose ASA for cardioprotective effects plus either a COX-2 inhibitor or NSAID.

M. Antiplatelet Use in the Elderly: The pharmacodynamic effects of clopidogrel were reported not to differ in the elderly patients.[104] The effects of clopidogrel 75 mg once daily for 10 days was assessed in healthy young volunteers (n = 12), healthy elderly subjects (> 65 years; n = 10) and otherwise healthy elderly subjects with atherosclerosis, manifested by intermittent claudication (n = 10). Inhibition of platelet aggregation and prolongation of bleeding time were similar among the three groups. However, the area-under-the-curve (0-24hr) values in the two elderly groups were two-times that of the younger subjects.

A prospective analysis of one acute care institution documented the use of clopidogrel and ASA in elderly patients hospitalized with acute coronary syndromes.[105] A total of 177 patients with mean (SD) age of 78 (6) years were included. Compared to use before hospitalization, at hospital discharge the use of ASA increased from 43% to 84% ($p < 0.001$); the use of clopidogrel also increased (from 21% to 54%; $p < 0.001$).

Another prospective analysis of a 12-hospital group reported antithrombotic medication use after stroke in the elderly patients.[106] A total of 377 patients with a mean (SD) age of 69.3 (11.1) years were assessed between mid-1995 and early 1998. Six months after the stroke, 42% were receiving ASA; ticlopidine use was 16%.

ASA use was reported among 61% of elderly patients (> 65 years; n = 76) admitted to a skilled nursing facility after experiencing a stroke between 1997 and late 1998.[107] Ticlopidine use was only 10.5% (clopidogrel was not marketed at the time of the analysis).

N. Selecting a Non-ASA Antiplatelet Agent: According to the literature, ASA is the preferred antiplatelet agent for most patients. However, some patients may be intolerant or sensitive to ASA. The number of therapeutic options has increased over the past decade, providing the practitioner with options. At the same time, some confusion may present in light of each pharmaceutical company promoting their product. An assessment of the published literature has been provided and comments are provided below to assist in selecting a non-ASA antiplatelet agent.

Dipyridamole as a single agent is only FDA-approved as an adjunct to warfarin to prevent postoperative thromboembolic complications associated with the placement of mechanical heart valves. Dipyridamole has various unlabeled uses in combination with ASA that include reducing the development of thromboembolic complications in patients with mechanical prosthetic heart valves. This agent would not be considered the first alternative to ASA, primarily due to the lack of FDA-approved use for the majority of patients needing antiplatelet therapy, minimal published evidence supporting use and the multiple daily dosing requirement.

Ticlopidine has literature to document the antiplatelet effects and has been directly compared to clopidogrel in patients undergoing stenting procedures. Ticlopidine is a useful agent but is associated with reversible neutropenia; routine blood tests are recommended with this agent. The introduction of clopidogrel provided a more favorable option to ASA than ticlopidine. Neutropenia is not a listed box warning/contraindication with clopidogrel; in addition, clopidogrel is dosed once daily compared to twice daily for ticlopidine. Although ticlopidine is effective, the negative recommendations for ticlopidine and in favor of clopidogrel plus ticlopidine not documenting to be more favorable in African-Americans for stroke prevention limit ticlopidine use and is not preferred over clopidogrel.

The decision for an alternative to ASA is between clopidogrel and the combination product containing dipyridamole-ER plus ASA (DP-ASA). Clopidogrel has received broader FDA-approved uses compared to DP-ASA. Also, clopidogrel is dosed once daily compared to BID for DP-ASA. Furthermore, DP-ASA can not be crushed/chewed etc., thus limiting alternative dosing techniques. However, these may be minor issues in selecting one of these two agents over the other. Since both of these antiplatelet agents are indicated as secondary stroke prevention, an analysis of these two agents for this use follows.

Two pivotal trials evaluating clopidogrel and DP-ASA are the CAPRIE[30] and ESPS-2[78] studies, respectively. An assessment of these two studies has been prepared to assist in the selection of therapy for patients with stroke.[72] Within this report, the authors present an indirect comparison between these two agents and ticlopidine; the authors state the data were collected from indirect comparisons and presented as such. The results of this report (which are used in promotional materials) appear to favor DP-ASA over clopidogrel. Although both CAPRIE and ESPS-2 evaluated antiplatelet therapy as secondary stroke prevention, many differences are present between these two studies. The dissimilarities of these two trials may limit the direct comparison of relative risk reductions for stroke (and other measured outcomes). A comparison of these two studies in terms of design and results follows.

Characteristic	ESPS-2 Trial[78]	CAPRIE[30]
Primary endpoint	Stroke (fatal and non-fatal); Death (all causes); Stroke and/or death	First occurrence of ischemic stroke, MI or vascular death
Study Design	2 X 2 factorial design with multiple groups; Multinational (no North America)	Parallel comparison of 2 groups with multiple endpoints measured; Multinational (North America plus Europe)
Selected Inclusion Criteria	> 18 years of age Experienced TIA (< 24 hours) or Complete ischemic stroke (> 24 hrs) within 3 months	≥ 21 years of age Onset of symptoms ≥ 1 week but ≤ 6 month of neurological deficit
Power	80% to detect 25% RRR	90% to detect 12-13% RRR for primary endpoint (not stroke subgroup)
Patients	~1650 per group Qualifying event: 76% stroke; 24% TIA	~3200 per group with stroke as qualifying event
Follow-up	2 years	Mean follow-up was 1.91 years

Dropouts	29% vs. 22% with DP-ASA vs ASA; 15.9% vs. 8.6% due to adverse events	21.3% vs. 21.1% with clopidogrel vs ASA; 11.4% for both due to adverse events
Compliance	97% DP vs. 84% ASA	Both 91%

As displayed in the above table, these two trials had many differences. The patients in both groups were not exact. Patients may be enrolled in the CAPRIE trial up to 6 months after onset of stroke symptoms while only 3 months for the ESPS-2 study. Thus more stable patients may have been treated with clopidogrel. Also patients with TIA could be entered in the ESPS-2 trial but were not in the CAPRIE. In addition, various baseline patient demographics differed between the two groups. For instance, a higher portion of patients in the stroke subgroup of CAPRIE compared ESPS-2 were diabetic (~25% vs. 15.3%, respectively), had hypertension (65% vs. 61%) or hypercholesterolemia (37.5% vs. 22.9%). Furthermore, the CAPRIE study was not powered to detect differences in the subgroups. Another difference was the overall dropout rates and those due to adverse effects between the two studies. These factors are important to consider in evaluating clopidogrel to DP-ASA. Until studies are conducted that directly compare these two agents, the specific differences in reducing the adverse events can only be speculated.

O. Other Antiplatelet Agents: Pentoxifylline (Trental®) and Cilostazol (Pletal®)

1. Pentoxifylline (Trental®)

Pharmacology: Classified as a methylxanthine derivative. The exact mechanism has not been determined, but appears to stimulate prostacyclin release from vascular tissue. This agent also has several effects on erythrocytes (increases flexibility and reduces whole blood viscosity) and decreases plasma hypercoagulability.[108,109]

Indication: Treat intermittent claudication associated with peripheral vascular disease.[108]

Efficacy: Pentoxifylline appears to increase initial and intolerable claudication distances, plus reduce the severity and occurrence of paresthesia. Although, pentoxifylline does not appear more effective than placebo in relieving other symptoms that include cramping, pain during exercise, and tiredness.[25,109]

According to the ACCP guidelines for chronic extremity arterial insufficiency, results of studies do not consistently document a benefit with pentoxifylline. Although some patients who are unable to partake in exercise therapy may see an improvement in walking distances. Otherwise, "pentoxifylline should not be routinely used in patients with intermittent claudication (grade 1B)."[25]

2. Cilostazol (Pletal®)

Pharmacology: Classified as a quinolinone-derivative selective phosphodiesterase inhibitor; this agent inhibits platelet aggregation and vasodilates arteries.[110,111]

Indication / Contraindication: Treat intermittent claudication; this agent is contraindicated in patients with congestive heart failure.[110]

Efficacy: Placebo-controlled trials report increases in initial and intolerable claudication distances. In addition, walking distances were increased greater with cilostazol than placebo. Limited data are available comparing cilostazol to pentoxifylline, in which the former agent may improve walking distances greater than the latter agent.[25,111]

According to the ACCP guidelines for chronic extremity arterial insufficiency, "For patients experiencing disabling claudication, particularly when lifestyle modification alone is ineffective and revascularization cannot be offered or is declined by the patient, we recommend a trial of cilostazol therapy (grade 2A). Cilostazol is not recommended for routine use in all patients with intermittent claudication because of its high cost and modest clinical benefit."[25]

P. Summary: The following summarizes the uses of each antiplatelet agent:

ASA:

- Primary agent recommended as the antiplatelet agent of choice in the guidelines.

Clopidogrel:

- Primary use is in combination with ASA in patients with unstable angina (whether patient will undergo PCI or medical therapy only); data indicate use of clopidogrel/ASA combination for 1 year after event (i.e., PCI).
- Also useful for use in combination with ASA in patients undergoing PCI; data indicate use of this combination for 1 year after the procedure.
- Otherwise recommended as alternative to ASA for patients allergic to or who have GI intolerance to ASA.
- A cost-effectiveness analysis concluded ASA is significantly more cost-effective than clopidogrel in patients able to take ASA.
- A few studies directly compared clopidogrel to ticlopidine in patients undergoing PCI. The data were analyzed 14-28 days after the procedure. No consistencies among the study results were documented; some studies reported a lower incidence of the adverse event with one agent while the opposite was reported in another study. Although, the studies did report some efficacy similarities between these two agents.
- According to the subgroup analysis, clopidogrel was no better than ASA in patients with either stroke or MI as qualifying event; clopidogrel may be preferred over ASA in patients with peripheral vascular disease and intermittent claudication to reduce ischemic complications (but this subgroup analysis was not powered to detect difference between ASA and clopidogrel).
- Study results evaluating clopidogrel in patients with HF have not been published at this time.

Ticlopidine:

- Major limitation to prescribing this agent is the higher incidence of clinically significant adverse effects compared to clopidogrel (i.e., neutropenia).
- Recommended only as an alternative to ASA; can be considered alternative to clopidogrel.
- No more effective than ASA in African-Americans in reducing adverse events.

ASA/Sustained-Release Dipyridamole:

- Only one clinical trial published evaluating this specific formulation.

- Results indicate this combination reduces stroke risk better than ASA.
- Debate is “ongoing” regarding the optimal minimal ASA dose for stroke: 50 versus 75 mg/day.
- A meta-analysis of 287 randomized trials concluded that the reduction in vascular events was comparable for ASA doses 75-150 mg daily and 160-325 mg daily; however, ASA daily doses of less than 75 mg had less benefit.
- Appears to be an alternative agent in patients unable to tolerate clopidogrel.

Dipyridamole:

- Indicated only in mechanical valve replacement in combination with warfarin.
- Literature does not recommend dipyridamole for all these patients, but considers ASA to be a better agent if an additional agent is added to the therapeutic regimen.
- Most disease guidelines do not include dipyridamole as an antiplatelet agent of choice or as an alternative; a few guidelines state dipyridamole may be harmful in selected disease states.

Pentoxifylline

- Indicated to treat intermittent claudication.
- Guidelines do not recommend routine use.

Cilostazol

- Indicated to treat intermittent claudication.
- Guidelines do not recommend routine use; reserve for patients with disabling claudication and not responding to lifestyle modifications and revascularization cannot be offered or declined by the patient.

Q. Recommendation for Anti-Platelet Review: No Brand Name antiplatelet medications are recommended for preferred drug status. Clopidogrel appears to be safer than ticlopidine (i.e., no neutropenia). However, the literature does not consistently support clopidogrel or ASA/dipyridamole-ER as superior agents compared to ASA. In addition, the medical literature recommends ASA for more disease states than either clopidogrel or ASA/dipyridamole-ER.

R. References: On file

2. Antidepressant Agents

A. Products: The following table displays the available antidepressant agents.

Class	Generic Name	Brand Example	Generic Avail
Tricyclic:			
Tertiary amines	Amitriptyline	Elavil	Yes
	Doxepin	Sinequan	Yes
	Imipramine	Tofranil	Yes
	Trimipramine	Surmontil	No
Tricyclic:			
Secondary amines	Desipramine	Norpramin	Yes
	Nortriptyline	Pamelor/Aventyl	Yes
	Protriptyline	Vivactil	No
Tricyclic-Like:	Amoxapine	Asendin	Yes
	Maprotiline	Ludiomil*	Yes
Triazolopyride	Trazodone	Desyrel	Yes
Phenylpiperazine	Nefazodone	Serzone	No
Serotonin/Norepinephrine Reuptake Inhibitor	Venlafaxine	Effexor	No
	Venlafaxine-ER	Effexor-XR	No
Aminoketone	Bupropion	Wellbutrin	Yes
	Bupropion-SR	Wellbutrin-SR	No
Tetracyclics	Mirtazapine	Remeron	No
Monoamine Oxidase Inhibitors	Phenelzine	Nardil	No
	Tranylcypromine	Parnate	No
	Isocaboxazid	Marplan	No
Selective Serotonin Reuptake Inhibitors	Citalopram	Celexa	No
	Escitalopram	Lexapro	No
	Fluoxetine	Prozac	Yes
	Fluvoxamine	Luvox	No
	Paroxetine	Paxil	No
	Sertraline	Zoloft	No

* No longer brand name in US

B. Guidelines: Upon consideration of the initial therapeutic treatment for depression, it is imperative for the first step of the treatment process to be proper diagnosis of the disease state itself. The practitioner should understand the context of the symptoms (i.e., biological, psychological, and social factors) that are encompassed in the patient's presentation.[1] The practitioner should also perform an assessment to determine the type, severity and duration of the depressed episode because treatment will be based upon the type of depression, current severity, duration and history.[2,3] For the initial treatment of depression, the first step is patient education. Patient and family education should include an explanation of depression and the concept of depression, lifestyle changes that may assist recovery (i.e., identified stressors and supports), expectations for response, and adherence to the treatment regimen as well as early signs of relapse.[1-3] Treatment goals depend on the phase of treatment. In the acute phase of treatment, the goals are to reduce

symptoms and improve quality of life (response and remission).[1] The goal for the maintenance phase is to prevent return of depressive symptoms (relapse/recurrence).[1]

For initial drug therapy, the effectiveness of antidepressant medications has been shown to be comparable between classes and within classes of medications.[3] Regardless of the initial choice of drug, most patients will have a therapeutic response ranging from 60-70%.[4-8] Therefore, the initial selection of an antidepressant drug will be based primarily on side effects profile, safety and tolerability, patient preference, cost and type of depression.[3] In considering drug therapy, a good approach is to use newer and less toxic drugs for **mildly and moderately depressed** patients while using drugs that act on both serotonergic and noradrenergic neurotransmitters, such as tricyclic antidepressants (TCAs) or velafaxine, in **severely depressed** patients.[9] For general treatment of **moderate depression**, choices include SSRIs[3] or TCAs.[2] **Chronic depression/dysthymic disorder** may use SSRIs and TCAs.[2,10] Severe depression (uncomplicated) can use SSRIs, venlafaxine, TCAs.[2,10,11] In patients with **severe depression** with melancholia, TCA or venlafaxine should be considered.[2,10-13]

Other disease states present in patients with depression should be considered in selecting an antidepressant agent. Agents of choice for patients with **cardiovascular diseases** (e.g., heart conduction disease, orthostatic hypotension, ventricular arrhythmias, and/or ischemic heart disease) are SSRIs (e.g., fluoxetine, sertraline, and paroxetine) and buproprion since these agents have minimum to no effect on heart rate, rhythm, or blood pressure.[14-16] Alternatively, a TCA can be used, but this is not first-line therapy. Preferred agents in patients with a **neurological disease** (e.g., seizures) are desipramine, SSRIs, trazodone or MAOIs; however, maprotiline, clomipramine, and bupropion should be avoided.[14,15] Patients who have experienced a stroke develop depression as a common sequela; SSRIs are preferred in this patient type.[14] SSRIs also are preferred in patients with Parkinson's disease.[14] Patients suffering from allergic disease may benefit from doxepin, trimipramine, amitriptyline, and maprotiline due to their strong antihistamine properties.[14] Patients with peptic ulcer disease may obtain some benefits from trimipramine and doxepin because of strong anticholinergic and histamine-2 antagonistic activity.[14] Patients who have sexual dysfunction should avoid TCAs, SSRIs, and MAOIs; buproprion has a lower incidence of erectile dysfunction, and alternatively, trazodone, nefazodone, or mirtazapine may be used.[14,15] Patients with existing ophthalmic disease should use antidepressants with little or no anticholinergic effects.[14] In the geriatric population, the drug of choice is based on side effect profile since efficacy among the agents are similar; antidepressants with low or no anticholinergic properties are preferred such as SSRIs, desipramine, nortriptyline or buproprion.[14] Also, use lower doses of antidepressants in the elderly because the geriatric population metabolize and excrete drugs slower.[14]

Treatment failure is defined as less than 50% reduction in symptoms on a depression rating scale such as the Hamilton Rating Scale for Depression of Montgomery Asberg Depression Rating scale during the first 4 to 8 weeks of therapy.[9,11] In consideration of treatment failure, two concerns are apparent to the health care provider: to stop the medication at the earliest point at which patient has minimal or no chance of responding; and if some benefits are present, but remission has not occurred.[17] Optimal improvement of symptoms is seen in ~4 weeks of initiation of therapy, and 25% to 33% of depressive episodes that do not respond by 4 weeks should do so by 8 weeks.[7,17]

C. Tricyclic Antidepressants (TCAs)

1. **Efficacy:** Although an individual patient may respond better to one agent than another, as a class, the TCAs are equally efficacious in equivalent doses.[18-22] These agents may be prescribed as first-line therapy for the treatment of depression.[2,3,9,18-20,22,23] TCAs exert a pharmacological effect by blocking the reuptake of the neurotransmitters serotonin and/or norepinephrine into the presynaptic neuron, thus increasing neurotransmitter availability at the postsynaptic receptor. The TCAs have broad activity and are effective for treating all depressive subtypes.[20,21] However, these agents are believed to be most effective for the treatment of severe melancholic subtypes of major depression.[2,10-13] The onset of action with the TCAs is delayed and patients should be informed that effects may not be seen for several weeks.[18-21,24] Patients should be given a thorough explanation of common side effects before treatment begins and should be encouraged to continue with treatment.

2. **Safety:**[18-26] Adverse effects associated with TCAs include anticholinergic, cardiovascular and CNS effects and weight gain. However, tolerance usually develops over the course of therapy to sedative and anticholinergic effects and postural hypotension. Therefore, TCAs should be started at low doses to minimize these effects and the dose should be increased gradually until the desired response is obtained. An agent with low anticholinergic activity (secondary TCA) should be selected initially.[9,10] Although the same adverse effects have been reported for each TCA, there is a possibility that each agent may cause other unique adverse effects.

   The most common side effects of the TCAs are anticholinergic effects that include sedation, insomnia, sexual dysfunction, blurred vision, constipation, dry mouth, tachycardia and urinary retention. In addition, cardiovascular effects such as postural hypotension, myocardial depression, arrythymias, tachycardia and electrocardiograph changes (prolongation of the QRS and QT intervals and ST-T wave changes) can occur. Adverse GI effects that have been reported in patients receiving TCAs include anorexia, nausea and vomiting, diarrhea, abdominal cramps, increase in pancreatic enzymes, epigastric distress and stomatitis.

   TCAs lower the seizure threshold and should be used with caution in patients with a history of seizure disorders, organic brain disease or who may be predisposed to seizures. In addition, caution should be exercised when using TCAs in patients with cardiovascular disease and in patients for whom excess anticholinergic activity could be harmful (presence of benign prostatic hypertrophy, history of urinary retention or increased intraocular pressure). TCAs have been associated with death by drug overdose in the United States and care should be taken when prescribing these agents to patients who exhibit suicidal ideation.

   TCAs are relatively contraindicated in patients who exhibit symptoms of angle-closure glaucoma. In addition, the concurrent use of MAOIs with TCAs is a relative contraindication. Furthermore, alcohol and barbiturates may potentiate the toxicity of these medications and concomitant use with all TCAs is contraindicated.

   Lastly, TCAs should not be terminated abruptly in patients who have received high doses for prolonged periods of time to avoid possible precipitation of withdrawal symptoms.

3. TCA Subclasses: TCAs are divided into two subclasses: tertiary and secondary. Although efficacy between these two subclasses is equivalent, a noticeable difference in adverse effect profile exists.

A. Tertiary Tricyclic Antidepressants

1. Overview: The tertiary TCAs are equally efficacious in equivalent doses.[18-21] The four tertiary TCAs (amitriptyline, doxepin, imipramine and trimipramine) exert more sedation, anticholinergic effects, orthostatic hypotension and serotonin blocking activity than the secondary TCAs. Tertiary amine antidepressants are demethylated *in vivo* to secondary amines that are relatively selective for norepinephrine reuptake inhibition over tertiary TCAs.[18-21]

2. Safety: The following table illustrates the adverse effect profile of the tertiary TCAs. According to this table, all four agents are associated with moderate to high severity for most of the adverse effects.[19]

Agent	Anticholinergic Effects[#]	Sedation	Orthostatic Hypotension	GI* Distress	Cardiac Arrhythmias
Amitriptyline	++++	++++	++++	0	+++
Doxepin	+++	++++	++	0	++
Imipramine	+++	+++	++++	+	+++
Trimipramine	+++	++++	++	0	++

++++ high; +++ moderate; ++ low; + very low; 0 none

[#] Dry mouth, blurred vision, urinary hesitancy, constipation * Gastrointestinal

3. Dosing: The usual dosage range for the tertiary TCAs are provided in the following table. Usually, the initial starting dose is low and gradually increased until the desired response is obtained.[19,22,24] Although the tables illustrate the "common" dosage range, each patient's dose should be individualized based upon response and adverse effects. The dose is usually administered once daily (at bedtime). The cost per month of these agents is relatively inexpensive

Agent	Brand name	Daily Dose (mg / day)
Amitriptyline	Elavil	10 - 150
Doxepin	Sinequan	10 - 150
Imipramine	Tofranil	10 - 50
Trimipramine	Surmontil	25 - 200

B. Secondary Tricyclic Antidepressants

1. Overview: The three secondary TCAs are equally efficacious in equivalent doses; however, these agents appear to have a higher remission rate than the tertiary TCAs.[22] The three secondary TCAs (desipramine, nortriptyline and protriptyline) exert less sedation, anticholinergic effects and orthostatic hypotension

than the tertiary TCAs. Secondary TCAs have greater norepinephrine activity and a greater seizure threshold than tertiary TCAs. Therefore, the secondary TCAs are usually recommended first over a tertiary TCAs due to the "improved" safety profile of the secondary.[19,20,22]

2. Safety: The following table illustrates the adverse effect profile of the secondary TCAs. According to this table, all three agents are associated with a less severe adverse effects than the tertiary TCAs.[19]

Agent	Anticholinergic Effects[#]	Sedation	Orthostatic Hypotension	GI* Distress	Cardiac Arrhythmias
Desipramine	+	+	++	0	++
Nortriptyline	+	+	++	0	++
Protriptyline	++	+	++	0	++

++++ high; +++ moderate; ++ low; + very low; 0 none

[#] Dry mouth, blurred vision, urinary hesitancy, constipation * Gastrointestinal

3. Therapeutic Monitoring: Plasma concentrations of TCAs, in general, vary greatly among patients due to genetic factors (e.g., hepatic metabolism) and physiochemical properties of the medication (e.g., lipid solubility). However, nortriptyline appears to have a well-defined "therapeutic window" at 50 - 150 nanogram/mL of plasma. Other therapeutic plasma concentration ranges which are generally accepted include desipramine (150 - 250 nanogram/mL) and imipramine (200 - 250 nanogram/mL).[19,20,22,24]

4. Dosing: The usual dosage range for the secondary TCAs is provided below in the following table. Usually, the initial starting dose is low and gradually increased until the desired response is obtained.[19,20,24] Although the tables illustrate the "common" dosage range, each patient's dose should be individualized based upon response and adverse effects. The dose is usually administered once daily (at bedtime). The cost per month of these agents is relatively inexpensive but more than the tertiary TCAs.

Agent	Brand name	Daily Dose Range (mg / day)
Desipramine	Norpramin	10 - 300
Nortriptyline	Pamelor/Aventyl	10 - 150
Protriptyline	Vivactil	5 - 60

4. Summary: The TCAs are effective agents for the treatment of various types of depression and can be used as first-line therapy for depression.[20-22,24] Although no difference in efficacy can be observed within the two subclasses of TCAs (administered at equipotent doses), the secondary TCAs may produce a better remission rate than the tertiary TCAs.[22] In addition, the severity of adverse effects produced by the secondary TCAs is less than the tertiary TCAs (however, the secondary TCAs are still associated

with adverse effects).[18-26] The acquisition cost of the generic (multi-source) TCAs is relatively inexpensive.

5. **Recommendation for TCA Review:** More similarities than differences in efficacy, safety and dosing are present among the tertiary TCA agents; the same can be stated for the secondary TCAs. Many in-distinguishable clinical drug characteristics are present between the multi-source and Brand Name agents within each tertiary and secondary TCA subclass. Brand Name TCAs are not recommended for preferred drug status. However, the Brand Name TCAs can be considered for preferred drug status if the price of the Brand Name agents are competitive to the multi-source (i.e., generic) formulations. The price "competitive" point will be determined by AL Medicaid.

D. Tricyclic-Like Agents

1. **Maprotiline:** A tetracyclic agent and is considered to be equally effective as TCAs. However, the incidence of seizures with this agent is higher than the TCAs. In addition, a bothersome rash occurs in approximately 5-10% of patients treated with this agent.[27] Maprotiline offers no advantage over TCAs in terms of efficacy and is associated with a higher incidence of seizures.

2. **Amoxapine:** Active metabolite of loxapine, an antipsychotic agent.[28] Amoxapine is useful in the treatment of neurotic depression, endogenous depression and mixed symptoms of anxiety and depression and has a similar efficacy compared to the TCAs. Although this agent is reported to have a quicker onset of action than the TCAs, this feature is not significant. Most clinicians avoid using amoxapine due to the side effect profile that includes extrapyramidal side effects, tardive dyskinesias, neuroendocrine changes and neuroleptic malignant syndrome. In addition, overdose with amoxapine is associated with a higher incidence of fatalities, seizures and tubular necrosis than other antidepressant agents.[27,29] Amoxapine offers no advantage over other antidepressants but potentially is more toxic.

3. **Recommendation:** No Brand Name medications from the tricyclic-like class are recommended for preferred drug status.

E. Trazodone (Desyrel®)

1. **Efficacy:** Trazodone is an effective antidepressant structurally unrelated to TCAs, SSRIs or MAOIs.[20,21,25] Data collected from controlled studies indicates that the efficacy of this agent is comparable to the TCAs and SSRIs in patients with major depressive disorder and other subgroups of depression. Similar to the TCAs and SSRIs, trazodone is a broadly effective antidepressant with no substantial evidence to support a unique spectrum of activity.[20] This antidepressant is useful in depressive disorders associated with insomnia and anxiety and is used effectively in the treatment of patients who have major depression with or without anxiety. In addition, trazodone does not aggravate psychotic symptoms in patients with schizophrenia or schizoaffective disorders.[20-22,24,25]

2. **Safety:** Trazodone does not possess the class I antiarrhythmic effects of the TCAs. This agent may be used in depressed patients with cardiac conduction diseases who can not tolerate SSRIs or TCAs. Although drowsiness, ataxia, nausea and vomiting may occur after acute overdose, serious cardiovascular and neurological toxic effects

are rare. Trazodone does not have quinidine like effects, but may aggravate ventricular ectopic activity, cause postural hypotension and is associated with the rare side-effect of priapism in males.[18-25]

Trazodone has dose-limiting problems of sedation and cognitive slowing or a "drugged" feeling. These adverse effects may limit the number of patients who can reach therapeutic doses for antidepressant response. The problem is compounded by the short half-life of trazodone (3 to 9 hours), which requires dosing to be divided into equal amounts given at least two to three times per day.[30] These features of this agent may contribute to noncompliance and subtherapeutic treatment which may affect remission rates in clinical practice. [20]

The low incidence of anticholinergic adverse effects and safety in overdose (compared to TCAs) makes trazodone an option for depressed patients including the elderly or suicidal patient. The sedative effect of this agent is useful in depressive disorders associated with insomnia and anxiety; also this agent may be used as a second drug for patients with SSRI associated sleep disturbances.[20,23]

The following table illustrates the adverse effect profile of the trazodone.[19]

Agent	Anticholinergic Effects[#]	Sedation	Orthostatic Hypotension	GI* Distress	Cardiac Arrhythmias
Trazodone	0	++++	+	+	+

++++ high; +++ moderate; ++ low; + very low; 0 none

[#] Dry mouth, blurred vision, urinary hesitancy, constipation * Gastrointestinal

3. **Dosing:** The usual dosage range for trazodone is 150 to 600 mg per day. The dose can be administered at bedtime.[31]

4. **Recommendation for Trazodone:** Trazodone is and its multi-source versions are effective for the treatment of patients who have major depression with or without anxiety. In addition, this medication has a mild side effect profile and is relatively inexpensive. The Brand Name medication can be considered for preferred status if the price of the Brand Name agent is competitive to the multi-source (i.e., generic) formulations. The price "competitive" point will be determined by AL Medicaid.

F. Nefazodone (Serzone®)

1. **Overview:** Nefazodone is indicated for the treatment of depression. This agent blocks 5-HT_2 receptors and inhibits the neuronal uptake of serotonin and norepinephrine.[32]

2. **Efficacy:** Results of studies indicate nefazodone to be an efficacious antidepressant.[3,10,14] Nefazodone is considered to be no different than SSRIs in treating this disease state.[33] The practice guidelines do not recommend this agent as an initial option to treat depression.[3,10] Nefazodone also is being evaluated for off-labeled uses that include anxiety, premenstrual syndrome, chronic pain conditions, and sleep disturbances.[34]

3. **Safety:** Nefazodone has a boxed warning regarding hepatic failure. The incidence is not frequent; 1 case resulting in death or transplant per 250,000-300,000 patient years of therapy.[32] Nefazodone has a unique side effect profile compared to the TCAs, namely few anticholinergic effects or sexual function disturbances.[32,35,36] While sustained hypertension has been reported with use of the venlafaxine-immediate release formulation, nefazodone use has been associated with possible postural hypotension in ~5% of studied patients and is listed as a precaution in the package insert.[32]

   Nefazodone inhibits the CYP 3A4 enzyme and modestly inhibits CYP 2D6; use in conjunction with triazolam, pimozide and carbamazepine is contraindicated. Nefazodone and MAO inhibitors should not be prescribed together. Wait 14 days after discontinuing MAO inhibitor before starting nefazodone; a 7 day wait period is recommended for nefazodone therapy converted to MAO inhibitor.[32,35,36]

   The most commonly observed adverse events associated with nefazodone (incidence of 5% or greater) are shown in the following table:[32]

Adverse Effect	Nefazodone	Placebo
Somnolence	25%	14%
Dry Mouth	25	13
Nausea	22	12
Dizziness	17	5
Constipation	14	8
Asthenia	11	5
Confusion	7	2

4. **Dosage:** The recommended starting dose for nefazodone is 100 mg BID. Dose increases should occur in increments of 100-200 mg/day (in 2 divided doses) at intervals of no less than 1 week based on tolerability and clinical response.[32] The effective dose range is generally 300-600 mg/day.[32,35]

5. **Summary:** Nefazodone is an efficacious antidepressant. Nefazodone may have fewer adverse drug reactions than the TCAs, but nefazodone may cause orthostatic hypotension in approximately 5% of patients. In addition, this agent has a boxed warning regarding hepatic failure and inhibits the CYP 3A4 enzyme. Nefazodone is dosed BID. Currently, none of the guidelines recommend nefazodone as initial therapy for depression.

6. **Recommendation for Nefazodone:** Nefazodone does not provide the practitioner with any advantages over the other antidepressants. In addition, some safety concerns are present with this agent. Nefazodone is not recommended for preferred drug status.

G. Venlafaxine (Effexor®, Effexor-XR®)

1. **Overview:** Venlafaxine is a bicyclic compound structurally unrelated to tri- or tetracyclic antidepressants or other marketed antidepressants. This agent inhibits neuronal uptake of serotonin, norepinephrine and to some extent dopamine. The pharmacological activity is similar to tricyclics, but has greater potency for blocking serotonin than norepinephrine or dopamine. Serotonin blockade of venlafaxine is similar to that of imipramine, while norepinephrine blockade is comparable to that of sertraline.[37,38]

2. **Indications:** Venlafaxine-extended release (venlafaxine-XR): Treatment of major depression, generalized anxiety disorder (GAD) and social anxiety disorder.[39]

3. **Efficacy:** Controlled trials have compared venlafaxine to active drugs that include TCA, trazodone and SSRIs.[40-42] Results of these trials document this agent to be an efficacious antidepressant agent; not all of the trials reported superior results with venlafaxine. Results of a non-blinded, uncontrolled study reported venlafaxine reduces depression symptoms in patients not responding to or had an unsustained response to SSRIs.[43] The guidelines/literature for treating depression recognize venlafaxine as a choice to treat this disease state, specifically for patients with more severe or resistant depression.[2,3-10]

   Venlafaxine-XR has been directly compared to a SSRI in a few studies. An overview of two studies evaluating venlafaxine-XR to fluoxetine in depressed outpatients follows. One double-blind study enrolled patients with concomitant anxiety;[44] SSRI non-responders may have been enrolled.[44,45] Patients with a minimum baseline score of 20 on the first 17 items of the 21-item HAM-D were randomized to either venlafaxine-XR 75 mg once daily (n = 128), fluoxetine 20 mg (n = 121) or placebo (n = 119). All doses were administered once daily for 12 weeks. The dose could be doubled at day 14; the dose could be increased again at day 28 to 225 mg and 60 mg, respectively. Patient baseline demographics were similar between the three groups. The mean age was ~42 years and ~60% of the participants were female. The mean scores of the primary endpoints (HAM-D Total, HAM-A Total, and CGI Improvement) were very similar between venlafaxine-XR and fluoxetine at all assessment time points. These scores were all statistically significant versus placebo at week 12. At week 12, no difference was measured between the two medication groups for the HAM-D response rate (≥ 50% decrease from baseline) and HAM-D remission rate (HAM-D score < 8). Week 12 was the only time point in which the HAM-A response rate (≥ 50% decrease from baseline) was higher for venlafaxine-XR than fluoxetine (~65% vs. ~50%; p = 0.037). The investigators also post-hoc analyzed the results via combining the HAM-D plus HAM-A response rate at week 12 (although this analysis method has not be validated[45,46]). The results suggest venlafaxine-XR 75 mg/day was no different than fluoxetine 20 mg/day (~77% for both). Although, response rates were greater with higher doses of venlafaxine-XR (150-225 mg/day) than fluoxetine (40-60 mg/day) (both p < 0.03). More patients in the venlafaxine-XR than fluoxetine group took chloral hydrate or zopiclone (52% vs. 40%) for sleep.

Another trial directly compared venlafaxine-XR to fluoxetine in outpatients with major depression.[47] Patients that did not have a ≥ 20% decrease in the HAM-D21 score during the screening phase (number not provided) were randomized to double-blind therapy of either venlafaxine-XR 75 mg once daily (n = 95), fluoxetine 20 mg (n = 103) or placebo (n = 97). All doses were administered once daily for 8 weeks. The dose could be doubled at day 14; the dose could be increased again at day 28 to 225 mg and 60 mg, respectively. Patient baseline demographics were similar between the three groups. The mean age was 40 years and 64-73% of the participants were female. Prior use of fluoxetine was present in 24% of the enrolled patients; 2% had received prior venlafaxine-XR. Almost 20% and 30% of the venlafaxine-XR and fluoxetine groups, respectively, discontinued the study; <10% of each group was due to adverse effects. The mean scores of the primary endpoints (HAM-D Total, MADRS total and CGI scores) were not different via the last-observation-carried forward analysis between the two medication groups. A few time points venlafaxine-XR was statistically significant better than fluoxetine (3 out of 12 assessment points) for the first two evaluation tools. A post-hoc analysis of remission rates on the HAM-D scale were higher with venlafaxine-XR than fluoxetine (~37% vs. ~22%; $p \leq 0.05$).

Results of a clinical trial reported venlafaxine to be no different than mirtazapine in hospitalized patients with severe depression with melancholic features.[48] However, only 157 patients were randomized to receive double-blind therapy for 8 weeks. More patients in the venlafaxine group dropped out because of adverse effects (15% vs. 5%; $p = 0.037$).

Two meta-analyses of venlafaxine clinical trials have been published and report greater efficacy (either higher remission rates and/or response via depression rating scale) than comparative antidepressants (e.g., SSRIs). One meta-analysis analyzed eight studies (not all published as full-text manuscripts; all studies conducted by Wyeth-Ayerst).[41] Either immediate-release (5 studies) or extended-release (3 studies) venlafaxine was compared to a SSRI (5 studies with fluoxetine; 2 with paroxetine); four of these studies included a placebo group. Final remission rates (total score of ≤ 7 on first 17 items of the HRSD) were calculated to be higher with venlafaxine than both the pooled SSRI results and placebo (45% vs. 35% and 25%, respectively). The majority of study participants were treated as outpatients (96.7%; n = 1977). The investigators do discuss study limitations that include short duration of study and patients were excluded if they failed prior SSRI therapy.

The other meta-analysis included 32 clinical trials that compared venlafaxine to other antidepressants that primarily included SSRIs (20 studies) and TCAs (9 studies).[42] The venlafaxine studies evaluated either the immediate- or extended-release formulation. Only 5 studies enrolled in-patient subjects. The studies totaled 5562 patients with a mean age of 48 years; 67% were female and the mean venlafaxine dose was 147 mg/day. The pooled standarized difference in mean treatment effect was greater with venlafaxine (effect size estimate, -0.14; 95% CI, -0.22 to -0.07). In addition, venlafaxine was associated with a high overall odds ratio for response (1.27; 95% CI 1.07-1.52) and remission rate (1.36; 95% CI, 1.14-1.61). After these results were analyzed via antidepressant class, venlafaxine had response rates only better than the SSRIs.

A meta-regression analysis concluded that antidepressant agents with pharmacological activity at more than one site do not provide greater efficacy rates than SSRI in treating

major depression.[49] This analysis included 105 clinical trials (published through 1997) that compared an SSRI and with an antidepressant drug that primarily effected serotonin and/or noradrenaline reuptake and/or serotonin antagonism. Less than 10 of these studies evaluated venlafaxine; the majority of studies included a TCA as the comparative antidepressant. A total of 11,537 patients were included in these trials; 5937 (51.5%) were treated with an SSRI. Fluoxetine was the most commonly evaluated SSRI; amitriptyline was the most commonly comparative antidepressant.

Studies at times may not have sufficient sample size to detect differences between the comparison groups. Meta-analysis, the statistical process of systematic reviews, is a method of combining results from "homogeneous" studies and statistically analyzing the results to determine an effect estimate. This is a useful analytical method, but proper techniques need to be incorporated and include: comprehensive and unbiased identification and inclusion of completed studies; definition of inclusion and exclusion criteria; uniform and unbiased data extraction processes; assessment of the heterogeneity of the individual study results; evaluation of the potential publication bias; and subgroup and sensitivity analysis.[50,51]

4. **Safety:** Venlafaxine use in combination with MAOI's is contraindicated. Sustained hypertension (treatment emergent increase in diastolic blood pressure of ≥ 90 mmHg≥ and ≥10 mm Hg above baseline for 3 consecutive on-therapy visits) has been reported in patients taking both venlafaxine-IR and ER formulations. Blood pressure should be monitored regularly.[39] Insomnia (up to 20%) and nervousness (up to 11%) are two side effects reported more commonly with venlafaxine. Other side effects include dry mouth (10-15%), abnormal male ejaculation (10-15%), dizziness (15-20%) and nausea (30%).[39]

   One clinical trial comparing venlafaxine-XR to fluoxetine reported the incidence of only one side effect to be lower with venlafaxine-XR (somnolence, 13% vs. 14%, respectively). The incidence of the other reported side effects were higher with venlafaxine-XR (exception was tremor; 10% for both) that included sweating (9% higher), insomnia (7% higher), nervousness (6% higher) and dry mouth (5% higher). Dizziness was most commonly reported and largest difference between the two medications (38% vs. 18%, respectively).[44]

   Another clinical trial directly comparing venlafaxine-XR to fluoxetine also reported dizziness to be a common adverse effect (26% vs. 6%, respectively); nausea was most common (36% vs. 20%, respectively) (both $p < 0.05$). The only adverse effect reported to be ≥ 5% with fluoxetine was diarrhea (14% vs. 19%; $p > 0.05$).[47]

   Serotonin syndrome has been reported with venlafaxine (via a pharmacodynamic interaction). Symptoms of this adverse effect include diarrhea, fever, diaphoresis, diarrhea and confusion.[52] Venlafaxine is metabolized by CYP 2D6 isoenzyme and does not inhibit CYP 3A4, CYP 1A2, and CYP 2C19.[39,40,53] Venlafaxine has not been reported to have clinically significant drug-drug interactions.[40,52-56]

5. **Dosing:** Daily venlafaxine-IR doses should be divided BID-TID; the total daily dose of venlafaxine-ER may be given once daily. The capsule contents of the venlafaxine-ER can be sprinkled on applesauce. Initial dose is 75 mg per day. A lower dose of 37.5 mg per day may be needed for some patients. The dose may be increased to 150-225 mg

per day; patients with severe depression may need up to 350 mg per day. Maximum daily dose to treat GAD and social anxiety disorder is 225 mg. Venlafaxine-ER should be taken with food; the capsule should not be chewed, crushed, etc.[39]

The typical venlafaxine dose appears to be > 100 mg/day. The weighted average venlafaxine dose was 147 mg/day according to the meta-analysis of 32 studies (which included the 8 studies of the other meta-analysis[41]). Six of these 32 studies had a mean venlafaxine dose of <100 mg/day; 3 of these studies evaluated a fixed dose of 75 mg/day. Five of the 32 studies enrolled in-patients; the mean dose ranged from 200-233 mg/day.[42] Only one published venlafaxine study was included in the meta-regression analysis report (this published study also was included in the other meta-analyses); doses in the unpublished studies included in the meta-regression analysis ranged from 75-269 mg/day.[49] The mean venlafaxine dose in the study evaluating this agent in SSRI nonresponders/ unsustained-response was 142 mg/day.[43] Compared to fluoxetine, the mean dose at week 12 was 140.8 mg and 39.9 mg, respectively, according to one trial[44] and 175 mg and 47 mg, respectively, at week 8 in another study.[47]

6. **Summary:** Venlafaxine is an efficacious antidepressant agent. National guidelines recommend this agent, specifically for more resistant cases of depression. Literature is available that documents patients failing an SSRI may respond to this agent. Venlafaxine-XR has a lower incidence of side effects than TCAs; hypertension, insomnia and nervousness are warnings/precautions with this medication. No significant drug-drug interactions have been reported with venlafaxine. The daily dose can be administered once daily with venlafaxine-XR. However, results from the reviewed clinical trials do not report superiority in efficacy or safety for venlafaxine-XR compared to fluoxetine. Only post-hoc or non-validated comparisons favored venlafaxine-XR. In addition, venlafaxine-XR was associated with a few disproportionally higher side effect incidences than fluoxetine.

7. **Recommendation for Venlafaxine:** Venlafaxine (both IR and ER formulations) is not recommended for preferred drug status. Brand Name venlafaxine formulations can be considered for preferred drug status if the price of the Brand Name agents are competitive to the multi-source (i.e., generic) formulations of the SSRI antidepressants. The price "competitive" point will be determined by AL Medicaid.

H. Bupropion (Wellbutrin, Wellbutrin-SR®)

1. **Pharmacology:** Involves the noradrenergic and/or dopaminergic systems; has weak inhibition of norepinephrine, serotonin, and dopamine uptake. [20,57,58]

2. **Indication:** Treatment of depression.[58]

3. **Efficacy:** Bupropion is an effective agent for the treatment of both inpatients and outpatients with major depression and the depressive component of bipolar disorder. This agent's efficacy is comparable to that of the TCAs, SSRIs and MAOIs. Treatment guidelines/literature recognize this agent as an effective agent to treat depression.[2,3,,22]

   The efficacy and safety of bupropion has been directly compared to fluoxetine in moderately to severely depressed outpatients with accompanying symptoms of anxiety.[59] Patients with a score of ≥ 20 the Hamilton Rating Scale for Depression (21

item) were randomly assigned to receive double-blind therapy of either bupropion (immediate-release formulation; 225-450 mg/day; n = 61) or fluoxetine (20-80 mg/day; n = 62). After 6 weeks of therapy, no statistically significant differences between the two groups for any of the efficacy variables were reported. The mean daily dose at the end of the study was 382 mg/day and 38 mg/day, respectively. There were no differences in adverse effects; each drug had higher incidence of selected side effects. The investigators concluded that bupropion is an efficacious antidepressant.

4. **Safety:** Bupropion has the following contraindications:[58]
Patients with a history of seizure disorder; current treatment with Zyban® (bupropion-SR); presence or history of bulimia or anorexia nervosa; or abrupt discontinuation of alcohol or sedatives (including benzodiazepines). Concurrent use with MAO inhibitors; at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with bupropion.

   Bupropion has a dose-related risk of developing seizures.[60] Dose titration is recommended with this agent and a maximum daily dose of 450 mg/day should not be exceeded due to the increase in seizure risk above this dose. The risk of this adverse effect is 0.4% at 450 mg/day, which is still higher than SSRIs, trazodone and low dose TCAs. Since most seizures associated with bupropion therapy have occurred during the absorption phase, peak plasma levels of the parent drug or one of its three active metabolites (or both) appear to be causativley involved in the pathogenesis of the seizure. Thus, bupropion should be administered on a divided dosing schedule to reduce the magnitude of peak plasma drug levels. In addition, no single dose should exceed 200 mg, and doses should be given no more often than every 4 hours.[58] The optimal dose is between 300 and 450 mg/day for most patients.[22,30,58] The bupropion-SR formulation appears to reduce the chance of seizures due to the slow release and absorption of this medications, thus reducing the maximum peak serum concentration. However, seizure risk is still possible with this formulation. Patients at risk for seizures with bupropion include: concurrent therapy with medications that lower seizure threshold (e.g., phenothiazines, TCAs[52,58]), excessive alcohol or sedative use; history of head trauma; diabetics treated with oral hypoglycemic agents or insulin; presence of severe hepatic cirrhosis.[58]

   Antidepressant therapy can be associated with sexual side effects; the incidence varies but appears to be up to approximately 30% of patients.[61-65] Studies evaluating the frequency of sexual side effects report bupropion (both IR and SR) to have an incidence of ~10-15% compared to ~30% with other antidepressants.[64,65] Thus bupropion may be a choice for patients who experience sexual side effects while taking other antidepressant agents; practitioners should recognize that sexual side effects may still occur with bupropion.

   Common side effects that are dose-related include agitation (9%), anxiety (6%), insomnia (16%), headache (24%), nausea (24%), dry mouth (18%) and dizziness (11%).[19,20,58] Weight loss is more common than weight gain. Bupropion is metabolized by CYP2B6 and inhibits CYP2D6.[58] The following table illustrates the adverse effect profile of the bupropion.[19]

Agent	Anticholinergic	Sedation	Orthostatic Hypotension	GI* Distres	Cardiac Arrhythmia

	Effects[#]		n	s	s
Bupropion	0/+	0/+	0	+	+

++++ high; +++ moderate; ++ low; + very low; 0 none

[#] Dry mouth, blurred vision, urinary hesitancy, constipation * Gastrointestinal

5. **Dosing:** The usual dose for bupropion-IR is 100 mg BID or 75 mg TID; doses up to 100 mg TID may be administered. Buproprion-SR may be initiated at 150 mg once daily and increased to 150 mg BID. The maximum daily dose is 200 mg BID.[57,58]

6. **Summary:** Bupropion is effective for the treatment of depression and may be used as first-line therapy in some patients. This agent has a warning/precaution regarding seizure potential plus being associated with agitation, anxiety, and insomnia. Bupropion has been reported to cause less sexual difficulties than other selected antidepressant agents. This agent inhibits the CYP 2D6 and the administration of selected medications may need to be adjusted. The sustained-release formulation is dosed twice daily. This agent does not offer any significant advantage in terms of efficacy and safety (in general).

7. **Recommendation for Bupropion:** The medical literature does not recognize bupropion as superior to SSRI antidepressant agents. Brand Name bupropion formulations are **not** recommended for preferred drug status. Brand Name bupropion formulations can be considered for preferred drug status if the price of the Brand Name agents are competitive to the multi-source (i.e., generic) formulations of the SSRI antidepressants. The price "competitive" point will be determined by AL Medicaid.

I. Mirtazapine (Remeron®)

1. **Pharmacology:** Mirtazapine is a piperazinoazepine-derivative tetracyclic antidepressant. This agent has many affects at various receptors. Noradrenergic and serotonergic activity is increased via antagonizing central presynaptic alpha-2 adrenergic receptors. This agent also antagonizes of serotonin type-2 and type-3 receptors, but has minimal affinity for serotonin types 1A or 1B. In addition, mirtazapine antagonizes histamine-1 receptors, moderately blocks alpha-1 adrenergic receptors and has a moderate antagonist effect at muscarinic receptors.[66,67]

2. **Indications:** Treatment of major depression.[68]

3. **Efficacy:** Results of clinical trials have reported mirtazapine to be an efficacious antidepressant agent. This agent appears to be similar in improving depression symptoms as other agents to treat this disorder.[33,67,69,70] Mirtazapine has been reported to be efficacious in patients who have failed initial SSRI therapy.[71] Mirtazapine also appears to be useful in patients with depression who present with anxiety symptoms and sleep disturbance.[70,72]

   Mirtazapine has been directly compared to fluoxetine in outpatients and inpatients with moderate to severe major depression.[73] Patients (non-North Americans) were randomized to double-blind therapy of either mirtazapine (15 mg in the evening; n = 60) or fluoxetine (20 mg once daily; n = 63) for 6 weeks. The daily dose could be increased to 60 mg and 40 mg, respectively. Patients were questioned regarding adverse effects

(i.e., no diaries were used). The mean age of the patients was ~47 years and ~57% were female; other baseline patient demographics were similar. Over 25% of the patients in the mirtazapine and fluoxetine groups discontinued therapy (26% vs. 31%, respectively); primary reason was adverse effects. The mean 17 HAM-D scores were no different at week 6 for the two groups; although at week 3 and 4, statistical significance was reported for mirtazapine. No other assessment endpoints were statistically different between the two groups at week 6. Also, no difference was reported for the number of CGI responders (63% vs. 54%; p = 0.677) at week 6. The mean dose during days 29-42 was 56 mg and 36 mg, respectively.

4. **Safety:** Mirtazapine may cause some orthostatic hypotension due to alpha-1 blocking activity. Sedation, increased appetite and weight gain are common with mirtazapine, most likely due to the H1-receptor antagonist effects.[66-69,70] Somnolence is the most commonly reported side effect (~50%); weight gain (~15%), increase in cholesterol plus triglyceride levels (~15%) and dizziness (~8%) are other commonly reported side effects. Dry mouth (~25%) and constipation (~14%) have been reported also with mirtazapine.[68] The incidence of sexual side effects has been reported to be much lower with mirtazapine than SSRIs.[74] Reports of mirtazapine use in patients with SSRI-induced sexual dysfunction have been published.[75]

   The side effects reported in a clinical trial comparing mirtazapine to fluoxetine also report drug mouth (18% vs. 5%, respectively) and somnolence (18% vs. 13%) as common side effects. Other commonly reported side effects included drowsiness (11% vs. 8%), blurred vision (8% vs. 2%), headache (9% vs. 18%) and nausea (3% vs. 10%).[73]

   Mirtazapine is a substrate for the CYP 3A4, CYP 2D6 and CYP 1A2 hepatic enzymes.[52,56] Results of in-vivo studies indicate mirtazapine is a much weaker inhibitor (10-900 times less) of these enzymes than “classic” enzyme inhibitors (e.g., ketoconazole).[67] Phenytoin and carbamazepine did reduce the mean serum mirtazapine levels (by almost 50%), but phenytoin and carbamazepine levels were not altered.[76,77] Neither levels of lithium or mirtazapine were affected by the combination of these two drugs.[78,79] The literature indicates that mirtazapine does not alter the pharmacokinetics of other medications.[70] Due to the affinity of mirtazapine for a variety of receptors, this agent may have pharmacodynamic drug-interactions.[52]

5. **Dose:** The initial dose is 15 mg once daily, usually at bedtime. Doses up to 45 mg once daily may be needed in some patients. Besides film-coated tablets, mirtazapine is available as orally disintegrating tablets. This dosage form does not need to be administered with liquid; however, the tablet should not be broken.[66,67]

6. **Summary:** Although selected antidepressant agents have affinity for more than one receptor, mirtazapine affects even more receptors. The pharmacological effects (e.g., sedation, weight gain) may be beneficial in some patients while bothersome in others. The national guidelines recognize mirtazapine as being efficacious to treat depression, but do not consider this agent as initial therapy for all patients. One study directly comparing mirtazapine to fluoxetine did not report a better response in terms of efficacy at the study endpoint for mirtazapine. One specific advantage of this agent is the oral disintegrating tablet formulation, which may be useful for **long-term care** patients and others with swallowing difficulties.

7. **Recommendation for Mirtazapine:** Mirtazapine is **not** recommended for preferred drug status.

J. Monoamine Oxidase Inhibitors (MAOI)

1. **Efficacy:** MAOIs are effective in the treatment of major depression, dysthymic disorders and atypical depression such as hypersomnia, hyperphagia and panic attacks. MAOI therapy should be started with a low dose, gradually increased and be administered for a period of 3-4 weeks before any significant improvement in depression is observed. This class of antidepressants is efficacious in the treatment of depression with social phobia. Some patients refractory to the TCAs, especially those with atypical depression or severe anxiety, respond to MAOIs.[23-25]

   These agents are not considered first-line therapy in the treatment of mood disorders because the risk of hypertensive crises due to drug-food and/or drug/drug interactions is significant.[23-25] However, recognition of the usefulness of these agents has increased with refinement of the definition and classification of the mood disorders and with greater understanding of the need to titrate doses carefully.

   Therefore, MAOIs have a place in the treatment of depression in selected patient types (i.e., refractory depression, panic attacks, social phobia). In addition, these agents may be used when anxiety accompanies depression and when patients exhibit atypical depression characterized by hypersomnia and/or hyperphagia.[25]

2. **Safety:** Adverse effects associated with the MAOIs include blurred vision, drowsiness, dizziness, weakness, trembling, decreased sexual function, diarrhea, nervousness, orthostatic hypotension, weight gain and tachycardia. However, MAOIs have a lower affinity for muscarinic-cholinergic receptors than the TCAs, and thus, these agents do not produce dry mouth, blurred vision and urinary retention.[24,25]

3. **Food and Drug Interactions:** The risk of hypertensive crisis due to drug-food or drug-drug interaction is higher with MAOIs than other antidepressants; patients need to avoid certain foods and drugs containing tyramine. Because all MAOIs have the potential to produce severe adverse reactions such as hypertensive crisis, hyperpyrexia and death, dietary restrictions and precautions regarding concomitant medications should be followed and vasoactive drugs should be avoided or administered in reduced dosage.[18-25]

   The MAOIs are involved with clinically significant drug interactions. A severe condition of hyperpyrexia can occur if MAOIs are taken in combination with high doses/overdoses of TCAs or meperidine. In addition, SSRIs and MAOIs should not be administered together. Since the SSRIs elevate serotonin levels, a serotonergic syndrome, characterized by tachycardia, hyperactivity, hypertension, and in severe cases, GI distress, tremulousness, hyperthermia, sweating and death by cardiovascular collapse, can occur.[80] Therefore, concurrent administration of an SSRI and an MAOI is contraindicated and a washout period of 2 weeks for shorter-acting SSRIs (paroxetine and sertraline) and up to 5 weeks for a longer-acting SSRI (fluoxetine) is recommended when switching from a MAOI to a SSRI or visa versa.[24,25,81]

Furthermore, MAOI may prolong and intensify cardiac stimulant and vasopressor effects (headache, cardia arrhythmias, sudden and severe hypertensive and hyperpyretic crises) of sympathomimetic agents. Thus, concurrent administration of a sympathomimetic agent and an MAOI should be avoided and a washout period of 2 weeks of the MAOI should occur.[24,25,82]

4. Dosing: The usual dosage range and cost per month of the MAOIs are provided below.

Agent	Brand name	Dose range (mg / day)
Isocarboxazid	Marplan	10 - 60
Phenelzine	Nardil	45 - 90
Tranylcypromine	Parnate	20 - 60

5. Summary: MAOIs are effective for the treatment of depression and have a role in therapy of comorbid anxiety and depression, atypical depression, panic disorder and bulimia. However, these agents are not widely recommended because of their unfavorable adverse effect profile, food/drug interaction potential and low therapeutic index. Therefore, no agent from this antidepressant class is recommended to be included on the preferred drug list.

6. Recommendation: No Brand Name MAO inhibitors are recommended for preferred drug status.

K. Recommendations for Antidepressant Review: No Brand Name antidepressants are recommended for preferred drug status.

L. References: On file.

3. Selective Serotonin Reuptake Inhibitors (SSRI)

A. Selective Serotonin Reuptake Inhibitors (SSRIs) Products: The available SSRI agents marketed in the US are listed below:

Brand Name	Generic Name	Generic Formulation
Celexa®	Citalopram hydrobromide	No
Lexapro®	Escitalopram oxalate	No
Luvox®	Fluvoxamine maleate	No
Paxil®	Paroxetine hydrochloride	No
Prozac®	Fluoxetine hydrochloride	Yes
Zoloft®	Sertraline hydrochloride	No

B. Pharmacology: The SSRIs exert a pharmacological activity by antagonizing the reuptake of post-synaptic serotonin. This action results in increased amounts of serotonin to interact with the receptors as opposed to directly stimulating the postsynaptic receptor.[1-5] Although each SSRI differs in the effect on serotonin, norepinephrine and dopamine, these

differences are either clinically insignificant or inconclusive (i.e., one SSRI can not be claimed to be therapeutically superior than the others).[1,6]

C. Indications: The following table displays the FDA-approved labeled[7-12] and unlabeled drug uses of the SSRIs:[13-15]

Agent	Depression	OCD*	Panic Disorder	Bulimia Nervosa	PDD+	PTSD‡	PE**	Other Uses
Citalopram (Celexa®)	X	UR	UL	UL	UL	UR	UR	Social phobia-UL
Escitalopram (Lexapro®)	X							-
Fluoxetine (Prozac®)	X	X	X	X	AP	UL	UL	Unlabeled uses: Bipolar Disorder Anorexia Nervosa Cataplexy Alcohol Dependence
Fluvoxamine (Luvox®)	UL	X		UL				-
Paroxetine (Paxil®)	X++	X	X++	UR	UL	X	UL	Generalized anxiety disorder-Labeled Social anxiety-Labeled Chronic headache-UL
Sertraline (Zoloft®)	X	X	X	UR	X	X	UL	Social Anxiety-Labeled Social Phobia-UL

*OCD = Obsessive-compulsive disorder
+PDD = Premenstrual dysphoric disorder
‡ PTSD = Post-traumatic stress disorder
**PE = Premature ejaculation
X = FDA-Approved labeled drug use
UR = Use reported
UL = Unlabeled drug use
AP = Another fluoxetine product (brand name Sarafem®) has received FDA-approval for this disease state.
++ = The controlled-release formulation is indicated for these conditions only

D. Efficacy: Controlled clinical trials have been published that directly compare one SSRI to another SSRI. Summaries of these studies are presented below.

Similar outcomes were reported for all efficacy measures and at all time points in primary care patients treated with either paroxetine, fluoxetine, or sertraline. In addition, the incidence of adverse effects and discontinuation rates were no different among the three SSRIs. Paroxetine, fluoxetine, and sertraline were similar in efficacy for depressive symptoms plus quality of life measurements.[16]

Sertraline and paroxetine exhibit a similar efficacy profile. In addition both medications were well-tolerated with no significant differences in treating major depression.[17]

Both sertraline and fluoxetine improved the efficacy variables (i.e., depression, anxiety, and quality of life) from baseline but the overall scores were not statistically different between the two groups. Also, both medications were well tolerated with no significant differences between treatments in treating outpatients with major depression.[18]

Paroxetine and fluoxetine were found to have comparable antidepressant efficacy (measured by the HAM-D and CGI scales). Also, anxiolytic activity (measured by COVI, STAI, and HAM-D scales) was no different between the two medications in treating major depression.[19]

Paroxetine and fluoxetine were no different in terms of antidepressant and antianxiety effects plus these two medications had similar safety and tolerability profiles in treating outpatients with major depression.[20]

No statistically significant differences were measured between sertraline and citalopram in general practice patients with major depression.[21]

Statistically significant clinical and quality-of-life improvements from baseline were observed in primary-care patients treated with either sertraline or fluoxetine, with no between-group differences.[22]

Citalopram was as effective as fluoxetine in the treatment of unipolar major depression (measured by changes in the MADRS and the HAMD mean total scores). Also, the adverse effect profile was similar with both medications being well tolerated in these general practice patients.[23]

Both sertraline and fluoxetine improved baseline scores of the HAM-DA in the treatment of major depression. Also, mean scores on the MADR scale, CGI scale, Zung Self-Rating Scale for Anxiety and the Leeds indicated no statistically significant difference between these two groups. Furthermore, the incidence of adverse effects was similar for both treatments in this 8-week, double-blind study.[24]

Sertraline and fluoxetine were reported to be equally effective and well tolerated in outpatients with major
depression and associated anxiety (assessed by the HAM-D and CGI scale). Both medications improved scores from baseline with no statistical difference between groups.[25]

Paroxetine was reported to be comparable to fluoxetine (assessed by the HRSD, MADR and CGI scales) after six weeks of therapy in patients with major depression.[26]

Citalopram and fluoxetine had no differences in the MADRS, HAM-D and CGI scores in outpatients with unipolar major depression after 8 weeks of therapy. Also, both agents were well tolerated with no significant differences in the side effect profiles.[27]

The above studies primarily evaluated the SSRIs in adult patients. A few studies have directly compared one SSRI to another SSRI specifically in elderly patients. A brief overview of these studies follows.

The efficacy and safety of sertraline and fluoxetine were evaluated in depressed elderly outpatients.[28] A total of 236 outpatients (≥ 60 years of age) who met DSM-III-R criteria for major depressive disorder were randomly assigned to 12 weeks of double-blind treatment with flexible daily doses of either sertraline (50-100 mg) or fluoxetine (20-40 mg). The primary efficacy measures were the 24-item HAM-D and CGI rating scales. Both medications produced a similarly response rate (73% for sertraline and 71% for fluoxetine). Both agents were safe and well tolerated. The investigators concluded that both medications are effective antidepressants for the treatment of depressed elderly outpatients.

A subgroup analysis was performed of geriatric patients enrolled in a clinical trial evaluating sertraline and fluoxetine.[29] Patients over age 70 years with a diagnosis of major depressive disorder were randomized to either sertraline (n = 42) or fluoxetine (n = 33) for 12 weeks. Improvements on measures of depression, including remission of depressive symptoms, were reported in both groups. More sertraline appeared to have better responses in two of the four tests. There was no difference in the rate of adverse effects experienced between the two groups. Although the investigators indicated a slightly better clinical response and lower side effects with sertraline, these data were obtained from a subgroup of patients consisting of a low number of patients being evaluated.

Paroxetine was directly compared to fluoxetine in depressed geriatric outpatients.[30] Patients (≥ 65 years of age) with an acute major depressive episode were randomized to receive double-blind therapy of either paroxetine (20-40 mg; n = 54) or fluoxetine (20-60 mg; n = 52) for 6 weeks. Efficacy was assessed by the 21-item HAM-D scale; cognitive function was assessed by use of the Mini-Mental State Examination (MMSE) and the Sandoz Clinical Assessment Geriatric Scale (SCAG). Both agents produced similar change from baseline in the mean HAM-D total scores ($p > 0.05$). Most commonly reported adverse effects involved the GI and nervous system, with no significant differences between treatments. The investigators concluded paroxetine and fluoxetine can reduce depression symptoms in the elderly patients.

Fluoxetine, sertraline and paroxetine were evaluated in an open-label study.[31] A total of 50 patients between the age of 80-98 years (mean age: 89 years) were followed for 12 weeks. Mean HAM-D scores were lowered with therapy (36%; 42% had at least a 50% decline in their scores). There were no significant differences in responses to the three antidepressants, and all drugs were well tolerated.

Paroxetine and fluoxetine were compared in elderly depressed patients.[32] A total of 106 patients (aged 61-85 years) were randomized to double-blind therapy for 6 weeks. Antidepressant efficacy was assessed using the HAM-D, MADRS, and CGI scales. Both agents demonstrated comparable efficacy. Also, no significant differences were reported between the two agents in either the tolerability or safety of treatment.

Not all patients initially treated with a SSRI may have the desired therapeutic outcome. In these patients, changing therapy to another SSRI may provide a positive clinical outcome. Although the number of patients was limited, clinical trials have been published documenting a therapeutic success with a second SSRI therapy after the first SSRI therapy was not useful. A brief overview of these studies is provided below.

Preliminary clinical trial information indicates that depressed patients not responding to the initial SSRI may respond to a second trial of another SSRI.[33]

Citalopram provided a clinical response in patients not responding to fluoxetine. Citalopram was associated with minimal side effects.[34]

Patients failing sertraline therapy had a clinical response to fluoxetine therapy. Also, fluoxetine was well tolerated.[35]

Based upon the results of the above studies, a greater efficacy outcome of one SSRI over another SSRI can not be stated (on average). However, individual responses do occur; if a patient does not respond to one SSRI, the patient may respond to another SSRI. The results of the clinical studies evaluating SSRIs plus practice experience with the SSRIs can be the reason that many published reports (i.e., therapeutic guidelines, position statements, review articles) have not stated that one SSRI agent is superior to another.[1-4,36-43] Limited clinical trials have been published directly comparing one SSRI to another in the elderly patients. The results of these trials plus extrapolating trial results from adult (i.e., non-elderly) patients do indicate that the elderly will have a therapeutic response to the SSRIs, but evidence is lacking in terms of which SSRI is clinically better in this patient group.[44-47] Although individual patient characteristics (i.e., age, medication profile) may be taken into consideration to select an initial SSRI for therapy, substantial evidence is not available to consistently support the enhanced efficacy of one SSRI over another.

E. Safety: As included in the studies[16-27] presented above, the types and incidences of adverse effects associated with the SSRIs are comparable. The primary adverse effects reported in patients taking a SSRI include insomnia, somnolence, dizziness, sexual dysfunction, nausea, headache, diarrhea and dry mouth. On average, the incidence of the side effects is similar among the SSRIs.[1,4,5,15,37,39,40,43-45] For instance, results of a study reported no statistically significant differences in the magnitude or frequency of sexual adverse side effects between sertraline and citalopram.[48] One study documented a slight difference in the risk of weight gain during extended therapy using paroxetine compared to fluoxetine (see below for further comments).[49] Individual patients may experience a difference in tolerability among the SSRIs[1,4,5,15,37,39,40,43-45]; a patient may not tolerate one SSRI but may tolerate another SSRI.[1,4,37] For example, a study reported that patients discontinuing fluoxetine due to side effects were successfully treated with sertraline.[50]

The low number of clinical trials directly comparing one SSRI to another SSRI in the elderly patients does not provide sufficient information to differentiate between these agents in terms of side effect severity. According to one clinical trial in the elderly, the tolerability of sertraline was similar to fluoxetine; however, fluoxetine was associated with a higher mean body weight loss (1.45 kg vs 0.77 kg, $p = 0.018$).[28] Paroxetine has been reported to have a higher anticholinergic side effect profile than the other SSRIs; although, the clinical disadvantage of this effect has not been consistently reported in the literature. Hyponatremia has been reported with the SSRIs, but again, the clinical differences between these agents have not been determined consistently.

Discontinuation Syndrome: The paroxetine package insert does contain a warning of abrupt discontinuation of therapy.[11] The paroxetine dose should be gradually reduced rather than abrupt cessation whenever possible. Side effects that include abnormal dreams, paresthesia and dizziness have been reported with abrupt discontinuation of therapy. The majority of patients experienced mild to moderate effects, which were self-limiting and did not require medical intervention.[11] Although this warning is present in the paroxetine package insert, similar events have been reported for other SSRIs (with the exception of fluoxetine).[51-55] In addition, case reports of sertraline causing

withdrawal symptoms have been published.[56-59] Although sertraline may be "marketed" as having a metabolite with low activity that prevents the emergence of withdrawal symptoms, published literature can not support this statement. The sertraline metabolite is clinically inactive and appears not to contribute to the pharmacological activity or risk of drug interactions.[5,12,60-65] Fluoxetine has a minimal chance to cause a withdraw syndrome due to a significantly longer terminal half-life than the other SSRI agents. However, the terminal half-life is similar among paroxetine, sertraline, escitalopram, and citalopram. Thus, the potential for a withdraw syndrome occurring with these four agents should not differ. The following table displays the terminal half-life of five SSRI agents. Based upon the information, symptoms can occur with any of these SSRI agents (except fluoxetine) after abrupt discontinuation.

SSRI	Mean Terminal Half-Life
Citalopram	~35 hours[7]
Escitalopram	27-32 hours[8]
Fluoxetine*	8.6 days[9]
Paroxetine	21 hours[11]
Sertraline	~26 hours[12]

*Measured as norfluoxetine, the major active metabolite

Weight gain: As mentioned above, paroxetine was documented to increase weight greater than sertraline and fluoxetine. One study evaluated the weight changes between these three SSRIs.[49] Although this one study reported a greater weight increase with paroxetine compared to the other two SSRIs, a few comments need to be considered in evaluating this study: 1) the change in body weight was based upon less than a total of 150 patients (approximately 46 patients each in the three groups); 2) the study reported that mean percent change in weight from baseline to endpoint was 3.6% for paroxetine and 1% for sertraline-based upon the mean baseline weight of the patients in these two groups (~77.2 kg), the actual mean weight gain was 2.78 kg for paroxetine versus 0.77 kg for sertraline, a 2 kg difference; 3) the study did report a greater number of patients treated with paroxetine had a ≥7% increase in weight than the other two groups-the actual results are 12 paroxetine-treated patients (25.5%) versus 2 sertraline-treated patients (4.2%) had a weight increase of 5.4 kg (7% of baseline body weight); 4) the mean change in weight gain was 2.78 kg for paroxetine-if 12 paroxetine-treated patients gained >5.4 kg, then some of the patients in the paroxetine group had a decline in baseline weight (although the same can be said for sertraline).

The study[49] can not be classified as a land-mark clinical trial to document that paroxetine causes "significantly" more weight gain than sertraline. Additional studies are needed to confirm these study results. The use of this single study (especially with a total study sample size of < 150 patients) to justify more weight gain with paroxetine is inadequate to differentiate weight gain between these two medications. After conducting a literature search, clinical trials evaluating paroxetine to other antidepressants were located (See Appendix A at the end of this report).[16,17,66-70] Although the primary focus of each of these studies was the efficacy of the antidepressants, changes in weight were reported in these studies. Based upon the data presented in these studies, paroxetine was not associated with a greater mean weight increase compared to the other antidepressants.

F. Drug-Drug Interactions: The following table displays the clinically significant drug-drug interactions with the SSRIs. According to this information, this class of medications have a few differences between the SSRIs.[71,72]

Agent	Brand Name	Cyproheptadine	Trazodone	MAOIs*	Thioridazine / Tolterodine	Tramadol
Citalopram	Celexa®			1		
Fluoxetine	Prozac®	2	1	1		3
Fluvoxamine	Luvox®			1		
Paroxetine	Paxil®	2		1	2	3
Sertraline	Zoloft®			1		

* Monoamine oxidase inhibitors Rating 1 = Severe and well documented interaction
Rating 2 = Moderate severity and probable documented interaction Rating 3 = Mild/moderate severity and probable documented interaction

A "serotonin syndrome" may occur with concomitant use of monoamine oxidase inhibitors (MAOIs). After discontinuation of SSRIs, allow at least 2 weeks prior to administration of a MAOI. Since fluoxetine has the longest half-life of the SSRIs, allow at least 5 weeks before starting MAOI therapy.[1,6] Paroxetine increases serum concentrations of thioridazine and may initiate ventricular arrhythmia.[5] The combination of tramadol and fluoxetine or paroxetine has been reported to produce serotonin syndrome. To avoid potential reduction of tramadol analgesic effect, fluvoxamine or sertraline should be consider.

The SSRIs as a class vary to some degree in the potential to have clinically significant drug-drug interactions.[73-76]

Fluoxetine, fluvoxamine and sertraline have been documented to inhibit the 3A4 cytochrome P450 isoenzyme; sertraline is a weak inhibitor of this enzyme compared to the other two agents. These three SSRIs may inhibit the metabolism of carbamazepine. Both fluoxetine and fluvoxamine may inhibit benzodiazepine metabolism; fluoxetine may cause QT prolongation with cyclobenzaprine.

Fluoxetine, paroxetine, and sertraline can inhibit medication metabolism by the CYP450 2D6 isoenzyme; sertraline is a weak inhibitor of this enzyme compared to the other two agents. All three SSRIs may inhibit the metabolism of antiarrhythmic agents (e.g., flecainide, mexiletine), tricyclic antidepressants, trazodone, non-atypical antipsychotic agents (e.g., haloperidol, chlorpromazine), and beta-receptor antagonists (e.g., propranolol, labetalol).

Case reports have been published documenting an increase in INR value with fluoxetine, fluvoxamine, paroxetine, and sertraline (to a much lesser extent) in patients taking warfarin. This interaction involves the CYP450 1A2 isoenzyme.

A few reports of increased phenytoin toxicity after fluoxetine therapy was initiated (via the CYP450 2C9 isoenzyme).

Citalopram has minimal potential to interact with the metabolism of medications; this agent has a low affinity for the CYP 2D6 isoenzyme.

G. Lexapro® (escitalopram oxalate): This SSRI is the S-enantiomer of racemic citalopram.[8] As indicated on page one of this review, escitalopram is indicated for depression only.[8] A

few clinical trials have been published evaluating this medication. Since this medication just has been marketed, more detailed information regarding this SSRI is presented.

Escitalopram Efficacy: A fixed-dose study was conducted to evaluate the safety and efficacy of escitalopram versus citalopram in reducing depressive symptoms.[77] Patients with a diagnosis of major depression entered a one-week placebo lead-in phase. Afterwards, patients meeting the criteria were randomized to double-blind, once-daily therapy of escitalopram 10 mg/day (n = 119), escitalopram 20 mg/day (n = 125), citalopram 40 mg/day (n = 125), and placebo (n = 122) for 8 weeks. The primary endpoint was the mean change from baseline in MADRS total score at 8 weeks. The average age of the study participants was ~40 years; approximately 65% were female and ~70% of the patients had a recurrent episode of depression. The mean changes from baseline for the MADRS total score were –12.8 vs –13.9 vs –12.0 vs –9.4 for the escitalopram 10 mg/day, escitalopram 20 mg/day, citalopram, and placebo groups, respectively. Mean changes form baseline in the HAM-D total score were –10.2 vs –11.7 vs –9.9 vs –7.6, respectively. Statistical significance was not demonstrated between escitalopram vs citalopram ($p = 0.09$); however, both active agents demonstrated efficacy compared to placebo ($p < 0.01$). Adverse effects resulting in discontinuation occurred in 4.2% vs 10.4% vs 8.8% vs 2.5% of patients, respectively. Most frequently occurring adverse events in the escitalopram treatment group are listed as follows: nausea, diarrhea, insomnia, dry mouth, and ejaculatory disorder. The investigators concluded that escitalopram 10 mg/day is efficacious and well tolerated.

Another trial was conducted to evaluate the safety and efficacy of escitalopram verses citalopram in reducing depressive symptoms.[78] Patients with a diagnosis of major depression (MADRS score 22 to 40) entered a one-week placebo lead-in phase. Patients meeting the criteria were randomized to double-blind, once-daily therapy of escitalopram 10 mg/day (n = 155) and citalopram 20 mg/day (n = 159) vs placebo (n = 154) for 8 weeks. The primary endpoint was the change from baseline in MADRS total score at 4 weeks. The average age of the study participants was ~43 years; approximately 77% were female. The mean change (± SE) in MADRS total score compared to placebo was –2.77 (0.56; $p = 0.002$) and –1.44 (0.86; $p = 0.095$) for escitalopram and citalopram, respectively. Adverse effects occurring in >10% of the study sample were nausea and headache. The investigators concluded that escitalopram and citalopram are well tolerated and have a similar adverse effect profile. Also, patients receiving therapy with escitalopram may experience a faster onset of effect compared to citalopram[78]; however, this study was not designed to determine onset of efficacy.[79]

A trial was conducted to evaluate the safety and efficacy of escitalopram versus placebo.[80] Patients with a diagnosis of major depressive disorder (MADRS score 22 to 40) entered a one-week placebo lead-in phase. Patients meeting the criteria were randomized to double-blind, once-daily therapy of escitalopram 10 mg/day (n = 191) vs placebo (n = 189) for 8 weeks. The primary endpoint was the change from baseline in MADRS total score at 8 weeks. The average age of the study participants was ~40 years; approximately 77% were female. The mean change from baseline in MADRS total score was –16.3 vs –13.6 in the escitalopram and placebo groups, respectively ($p = 0.002$). Adverse events occurring in >5% of the study sample were headache, nausea, and ejaculation disorder. The investigators concluded that escitalopram 10 mg/day is more effective than placebo, and is safe and well tolerated.

Escitalopram Safety: Compared to higher dose citalopram, escitalopram may have a lower to similar incidence of side effects. The most common side effect was nausea, occurring in 21%, 14%, 22%, and 6% of patients in the escitalopram 10 mg/day, escitalopram 20 mg/day, citalopram 40 mg/day, and placebo group, respectively. Diarrhea

(10%, 14%, 11%, and 7%), insomnia (10%, 14%, 11%, and 5%), and dry mouth (10%, 9%, 10%, and 7%) were other side effects reported.[77]

Another clinical trial comparing escitalopram, citalopram, and placebo indicated no difference in side effect profile. Nausea and headache was reported in >10% of each group (specific rates not provided).[78]

In a clinical trial evaluating escitalopram and placebo, nausea (3.7% vs 9.8%) was the only adverse effect demonstrating a statistical difference between treatment groups ($p < 0.05$). The most common side effect was headache, occurring in 10.1% vs 12% of patients in the placebo and escitalopram groups, respectively. Ejaculation disorder (0% vs 6%) was another side effects reported.[80]

The incidence of adverse effects appears to increase with an increase in the escitalopram dose. The following table displays the incidence (%) of common adverse events inpatients receiving placebo, escitalopram 10 mg/day, and escitalopram 20 mg/day.[8]

Adverse Effect	Placebo (n = 311)	Escitalopram 10 mg/day (n = 310)	Escitalopram 20 mg/day (n = 125)
Insomnia	4%	7%	14%
Diarrhea	5	6	14
Dry Mouth	3	4	9
Somnolence	1	4	9
Dizziness	2	4	7

The following table displays the incidence (%) of sexual adverse effects in placebo-controlled clinical trials.[8]

Adverse Effect	Escitalopram (n = 225 males)	Placebo (n = 188 males)
Ejaculation disorder (delay)	9%	< 1%
Decreased libido	4	2
Impotence	3	< 1
	Escitalopram (n = 490 females)	Placebo (n = 404 females)
Decreased libido	2%	< 1%
Anorgasmia	2	< 1

The adverse effect profile of escitalopram is similar other SSRIs. Adverse effects that may occur with escitalopram include: insomnia, diarrhea, dry mouth, somnolence, dizziness, diaphoresis, constipation, fatigue, indigestion, sexual side effects, decreased libido, and impotence.[8,81,82]

Escitalopram Drug interactions: A clinically significant interaction with escitalopram exists with MAOIs. As with other SSRIs, a 14-day washout period is required between therapy with a SSRI and a MAOI.[8] In-vitro studies demonstrate minimal inhibition of the CYP 3A4, -1C2, -2C9, and -2C19 isoenzymes. In-vivo data are limited; however, escitalopram does not appear to have clinically significant interactions with these isoenzymes.[8,83]

The following list of drugs or drug classes may potentially interact with escitalopram: alpha/beta antagonists, narcotic analgesics, SSRIs, beta blockers, carbamazepine, cimetidine, clozapine, warfarin, cyproheptadine, dextromethorphan, haloperidol, lithium, macrolide antibiotics, MAOIs, methadone, mexiletine, phenytoin, propafenone, protease inhibitors, risperidone, serotonin agonists, sibutramine, thioridazine, tramadol, tricyclic antidepressants, tryptophan, CYP2C19 inducers and inhibitors, and CYP3A4 inducers and inhibitors.[8,81,82] However, the clinical significance of these interactions has not been fully evaluated.

Escitalopram Dosing: Escitalopram 10 mg once daily in the morning or evening, with or without food. The dose may be increased to 20 mg once daily after one week of therapy. For elderly and patients with hepatic impairment, the dose of escitalopram is 10 mg once daily.[8]

H. Prozac® Weekly: Fluoxetine has been prepared into a once-weekly dosage formulation. The intent of this product is to enhance patient compliance in patients stabilized with once-daily fluoxetine therapy (due to the long half-life of fluoxetine). According to one study (approximately 55 patients per group), once-weekly fluoxetine was reported to have a higher compliance rate than once-daily fluoxetine (86% vs 79%, respectively).[84] In terms of efficacy, one controlled clinical trial evaluated once-weekly fluoxetine to once-daily fluoxetine and placebo. The 52-relapse rate (measured by the Kaplan-Meier plot) was highest with placebo followed by once-weekly fluoxetine and then once-daily fluoxetine (50% vs 37% vs 26%, respectively) ($p < 0.05$ for both fluoxetine formulations compared to placebo; p = NS for the fluoxetine comparison).[85] All other outcome measurements were no different between the two fluoxetine preparations (p = NS). According to the *Medical*

Letter, "More studies are needed to determine whether once-weekly fluoxetine is as effective and safe as taking smaller doss of the drug once daily. The 90-mg dose of *Prozac Weekly* may not be optimal for all patients, and dose titration will be difficult with the new formulation. Medical Letter consultants doubt that compliance will be better with once-weekly dosing."[86]

I. Pharmacokinetics in the Elderly: The following information describes the pharmacokinetic changes in elderly patients taking an SSRI.

Citalopram: In patients ≥ 60 years of age, the area-under-the-curve (AUC) and terminal half-life were increased by 23% and 30%, respectively, in multiple dose studies. Cmax (maximum serum concentration) was not changed. The initial starting dose in these patients should be reduced to 20 mg once daily.[7]

Escitalopram: In patients ≥ 65 years of age, the area-under-the-curve (AUC) and terminal half-life were increased by ~50%. The Cmax (maximum serum concentration) was not changed. The initial starting dose in these patients should be reduced to 10 mg once daily.[8]

Fluoxetine: The pharmacokinetics of fluoxetine possibility may be altered in the elderly (≥ 60 years of age). However, no unusual incidence of adverse effects has been observed in these patients. Also, a lower dose should be considered in the elderly patients. Due to the extensive half-life of the active metabolite, patients with a decrease hepatic function should be monitored more closely while taking this SSRI.[9]

Paroxetine: The Cmin (serum concentration prior to next dose) is increased by 70-80% in elderly patients compared to non-elderly patients. The initial starting dose in the elderly should be reduced to 10 mg once daily; the maximum daily dose is 40 mg.[11]

Paroxetine Controlled-Release: The pharmacokinetics were not evaluated in the elderly. The initial starting dose in the elderly should be reduced to 12.5 mg once daily; the maximum daily dose is 50 mg.[87]

Sertraline: Plasma clearance is reduced in elderly patients compared to non-elderly patients. Patients with hepatic impairment should receive a lower daily dose and be monitored.[12]

J. Dosing: The following table displays the usual dosing range and frequency of SSRIs in treating depression, panic disorder, and OCD for adults ≥ 18 years of age:[7-15]

Agent	Brand Name	Depression	Panic Disorder	OCD
Citalopram	Celexa®	20 - 40 mg once daily	20 - 30 mg once daily	-
Escitalopram	Lexapro®	10 - 20 mg once daily	-	-
Fluvoxamine	Luvox®	50 - 100 mg at bedtime	-	50 - 300 mg per day
Fluoxetine	Prozac®	20 - 80 mg once daily	10 - 60 mg once daily	20 - 60 mg once daily
Paroxetine	Paxil®	20 - 50 mg once	10 - 60 mg once daily	20 - 60 mg once

		daily		daily
Paroxetine-CR	Paxil® CR	25 - 37.5 mg once daily	12.5 - 37.5 mg once daily	-
Sertraline	Zoloft®	50 - 200 mg once daily	50 - 200 mg once daily	50 - 200 mg once daily

K. Summary: Since the primary use of the SSRIs is for the treatment of depression, only those SSRIs with a FDA-approved indication will be considered (thus fluvoxamine is excluded). Based upon the results of clinical trials, the SSRIs appear to be no different (on average) in terms of efficacy, safety and daily dosing. However, individual responses may occur and changing therapy to another SSRI may lead to a therapeutic response if the first SSRI was unsuccessful. In the elderly patients, the initial SSRI dose should be lower than the adult dose since this medication class is metabolized by the cytochrome P450 enzymes. One characteristic that may distinguish one SSRI from another is the drug-drug interaction profile. Citalopram, escitalopram and sertraline appear to have the least potential for drug-drug interactions among the SSRI class.

L. Recommendation for SSRI Review: More similarities than differences in efficacy, safety and dosing are present among the SSRI antidepressants. Many in-distinguishable clinical drug characteristics are present between the multi-source and Brand Name SSRI agents. Brand Name SSRIs are not recommended for preferred drug status. However, the Brand Name SSRIs can be considered for preferred drug status if the price of the Brand Name agents are competitive to the multi-source (i.e., generic) formulations. The price "competitive" point will be determined by AL Medicaid.

M. References: On file.

Appendix A
Weight Changes with Paroxetine Compared to other Antidepressants

The change in weight was a secondary endpoint of a trial comparing paroxetine, fluoxetine, and sertraline in the treatment of depression.[16] The study participants were primary care patients aged 18 years and older. The following table displays the change in weight among these patients. A specific weight gain definition was not provided.

Agents	Regimen	Duration	N	Patients with Weight Gain (%)
Paroxetine Fluoxetine Sertraline	20 mg once daily 20 mg once daily 50 mg once daily	9 months	189 193 191	2 (1) 0 (0) 1 (1)

Fluoxetine was compared to sertraline and paroxetine in outpatients with major depressive disorder or atypical major depressive disorder.[66] The patients were aged 18 years and older. The following table displays the change in weight among these patients. No specific changes in weight numbers provided.

Agents	Regimen	Duration	N	Mean Baseline Weight in kg (SD)	≥ 7% Increase from Baseline
Fluoxetine Sertraline Paroxetine	20-60 mg QD 50-200 mg QD 20-60 mg QD	10-16 weeks	63 70 67	72.4 (17.4) 75.6 (19.4) 76.3 (18.6)	1.6% 2.9% 9% p = 0.092

Sertraline was compared to paroxetine in outpatients with unipolar major depression aged 18 years and older.[17] The following table displays the change in weight among these patients. No p-values were included in the study for weight change.

Agents	Regimen	Duration	N	Mean Weight Gain (lbs)	Patients with Weight Gain (%)	Patients with Weight Loss (%)
Paroxetine Sertraline	20-40 mg QD 50-150 mg QD	24 weeks	176 177	2.9 1.3 p = NS	33.1 20.2	6.9 12.4

Paroxetine was compared to mirtazapine in outpatients with major depressive disorder aged 18 years and older.[67] Mean baseline weight (SD) for mirtazapine group men, 81.3 ± 11.4 kg; women, 69.5 ± 13.9 kg; mean baseline weight (SD) for paroxetine group men, 79.6 ± 11.8 kg; women, 69.3 ± 15.6 kg. The following table displays the change in weight among these patients.

Agents	Regimen	Duration	N	Mean Weight Change (kg) (SD)	Patient with ≥ 7% Weight Gain	Patients with ≥ 7% Weight Loss
Paroxetine Mirtazapine	20-40 mg/day 15-45 mg/day	6 weeks	134 135	- 0.2 (1.7) + 1.1 (2) p < 0.0001	0 10	3 0

Paroxetine was compared to bupropion sustained-release in outpatients with major depressive disorder aged 60 years and older.[68] The following table displays the change in weight among these patients.

Agents	Regimen	Duration	N	Mean Change in Weight (kg)
Paroxetine Bupropion SR	10-40 mg/day 100-300 mg/day	6 weeks	52 48	- 0.4 - 0.7

Paroxetine was compared to venlafaxine to treat inpatients or outpatients, with major depression less than 8 months, aged 18-60 years old.[69] The following table displays the change in weight among these patients. No specific numbers were given for weight change.

Agents	Regimen	Duration	N	Mean Baseline Weight (kg) SD)	Weight Change
Paroxetine Venlafaxine	30-40 mg/day 200-300 mg/day	28 days	62 61	68.9 (15.3) 67.6 (16.4)	p = NS p = NS

A naturalistic setting evaluated the efficacy of bupropion, moclobemide, paroxetine, sertraline, and venlafaxine in outpatients with unipolar major depressive disorder aged 18 years and older.[70] The following table displays the change in weight among these patients. No p-values were included in the study; no specific change in weight numbers provided.

Agents	Mean (SD) Daily Dose	Duration	N	Patients with Weight Gain (%)	Patients with Weight Loss (%)
Paroxetine Sertraline Venlafaxine Moclobemide Bupropion	18.7 (6.1) 105.4 (217.5) 81.4 (58.4) 370.8 (304.6) 143.3 (25.8)	8 weeks	55 37 62 24 15	11 5.4 9.7 0 13	3.6 11 8.1 13 20

Thus according to the published literature, the majority of the published paroxetine clinical studies document a minimal mean increase in weight or even a mean decrease in body weight.